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SYSTEMIC FACTORS IN CARCINOGENESIS*

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IN 1874, at a meeting of the Pathological Society of London, the question was raised whether cancer should be regarded as a local or a systemic disease. While Sir James Paget thought that cancer was a "disease of the blood," Sir William Gull, Hutchison and others maintained its strictly "local" origin.[26] An almost cyclic alteration of these thoughts can be traced in cancer research of the past 80 years. Experimental chemical carcinogenesis, although it contributed greatly to our understanding of the neoplastic processes, has swung the balance of the scale towards local or cellular factors and emphasis has been placed on the search for carcinogenic agents. Advances in biochemical and biophysical sciences made possible a more detailed analysis of the properties of the malignant cell and so diverted attention from the investigation of the nature of the systemic factors affecting neoplasia. Although so-called "cancer susceptibility" or "resistance" has always been mentioned as an important factor, the tendency was to regard the local action of chemical carcinogens as a model for the causation of spontaneous tumours. The nature of factors responsible for the development of spontaneous tumours in man was implied, on the basis of the effects of experimental carcinogens in animals. We were tempted to forget that apart from industrial carcinogenesis there is little evidence to implicate either chemicals or viruses in the etiology of common cancers in man, though Cook[10] a long time ago warned that the demonstration that chemicals can act as carcinogenic agents does not mean that they constitute a common tumour-inducing factor.

Only recently do we appear to have slowly reached the point where it is evident that both local and systemic factors are operational in neoplastic diseases, although obviously any systemic factor will finally act through a local medium. Many investigators have ceased to view cancer as an autonomous entity. This is largely the result of the demonstration that neoplastic growth can be modified by hormonal factors. By means of these factors, dependent and independent tumours were differentiated, the latter being those in which no factors able to modify growth have been demonstrated as yet. This has been an important development, which contributed to the disparagement of the concept of autonomy of cancer. However, probably no tumour is completely autonomous, since it is dependent at least on nutrition and possibly on other factors, known or unknown. The division into dependent and independent tumour is probably artificial and certainly meaningless without specification of the particular factors concerned.

The objective of our studies was to correlate the evidence available on the action of various systemic factors affecting the malignant process with our experience in chemical carcinogenesis. The term "systemic factors in carcinogenesis" was introduced in 1927 by Kreyberg,[40] who suggested the possibility of an indirect action of external carcinogens through a "systemic" (vascular) factor in addition to a local effect on the cells. The following discussion includes hormonal, neurotrophic and immunological factors; this appears to be the most obvious grouping of demonstrated and suggested factors. Confirmed experimental findings lead us to believe that systemic factors are involved in all phases of neoplasia in addition to the local ones. The word "systemic" denotes, probably more appropriately than other terms, the nature of these factors, implying both the "host" and a particular "system".

HORMONAL FACTORS

The participation of hormonal factors in the neoplastic process has long been recognized. One might refer here to the observations of Beatson[3] at the turn of the century on the effects of ovariectomy on breast cancer. However, it has only been during the last few years that the importance of endocrine factors in the development of malignant tumours has been appreciated to an increasing extent. The basic reorientation in the consideration

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of hormonal factors in neoplasia is probably directly related to the evidence that endocrine glands are principally involved in the etiology of several varieties of tumours. In 1932, Lacassagne[43] showed experimentally that œstrogens increase mammary tumour incidence in mice. Since then œstrogens have been demonstrated to participate in the induction and progression of a wide variety of tumours, including mammary, uterine, prostate, renal, vesical, adrenal, testicular, ovarian, pituitary, bony, and connective tissue tumours, lymphomas and leukæmias. The fact that the tumours not only of effector tissues, but also of other organs, are influenced by œstrogens brings up the question of a direct or indirect role of hormones in the neoplastic process. Ingle[39] has introduced the concept of "permissive action of hormones", suggesting that the action of some hormones may be only adjuvant to other factors permitting the effects to take place. Several instances of "permissive action" of hormones have been confirmed subsequently in experimental carcinogenesis. Griffin, Rinfret and Corsiglia[22] reported complete inhibition of liver damage and hepatoma formation after administration of 3′-methyl, 4′-dimethyl-aminoazobenzene to hypophysectomized rats; feeding of the dye to normal rats for 10-12 weeks was sufficient to induce a high percentage of tumours. Inhibition of liver tumour formation by 2-acetyl-aminofluorene in hypophysectomized animals was reported by us in 1953.[62] The interpretation of the inhibitory effects of hypophysectomy on hepatic tumour formation is difficult. Our results indicate that the inhibitory effect concerns not only the initial lesion in the liver, but also conversion of pre-existing lesions into malignant tumours. Two possible mechanisms might be considered: (1) A direct hormonal effect caused by removal of hormonal regulation of a target organ. Such an endocrine relationship with pituitary gland has not yet been demonstrated. (2) An indirect effect mediated through factors regulating liver metabolism. This includes pituitary factors regulating liver regeneration, such as those described by Glinos and Gey[18] and those regulating sex hormone metabolism.[9]

The concept of permissive action of hormones added weight to a postulate expressed by Gardner[16] that "the possibility that abnormal endocrine environments can create or destroy cancer seems remote – the hypothesis that abnormal endocrine environments may result in the expression of potentialities of the tissues, less likely to be expressed under a 'normal environment', seems tenable." Observations on animals with spontaneous tumours of endocrine glands show that tumours of non-endocrine organs may be dependent on some hormonal imbalance. For example, rats with spontaneously developed hypophyseal tumours showed thymomas, hepatic adenomas, carcinomas of the oral cavity, bronchial carcinomas, leukæmias and lymphosarcomas.[15] The incidence of these types of tumours in normal rats is low. An etiological relationship must be entertained.

The voluminous literature on the effects of hormones in neoplasia contains many contradictions. Some of them are explainable by the differences in specific conditions in which the experiments have been carried out; others are based on variability of interpretation; still others may be only apparent and will be resolved by further investigations. At present a systematic integration of the experimental and clinical findings appears to be impossible. Gardner[17] considered four factors in the analysis of hormonal responses in carcinogenesis: (1) variations in hormone production; (2) variations in the end organ sensitivity; (3) differences in the utilization, destruction or excretion of hormones; (4) presence or absence of augmenting or inhibiting influences. Suffice it to say that in many instances the interdependence of factors is not completely understood. The variations in hormone production are not always evident, and the hormones maintaining the neoplastic process might operate at physiological levels. Bethune,[4] for instance, reported normal œstrogen excretion levels in hypophysectomized patients, in whom the operation brought an objective remission of the tumour. No differences might be apparent in the end-organ sensitivity, though the responses vary. The importance of variations in the utilization or excretion of hormones, and the action of non-specific promoting or inhibiting factors, have also been stressed.

The development of hormonally "dependent" tumours usually requires a long period of time and passage through successive phases of hyperplasia and benign neoplasia. Undoubtedly a long "critical" period of hormonal dependence exists. The hormones maintaining the tumour growth in this phase might differ from those hormones which induced it. The progression of cancer, i.e. transformation of less malignant cells into more malignant ones, appears to be gradual and usually continues if the abnormal hormonal situation persists. In each instance any hormonal factor is apt to have its antagonist. This may be functional (such as a particular re-setting of events in the hormonal system), or chemical (such as steroid compounds originated by simple changes in the molecule of the original hormone, with subsequent acquisition of antagonistic action).

The perplexing combination of hormonal effects on tumour growth can be illustrated by the studies of actions of the adrenal cortex: its variety of hormonal functions affects to a certain degree the neoplastic process in any location. If adrenal cortical hormones are necessary for the function of all tissues (such as metabolism, secretion, growth),[59] one might expect that these hormones would also be involved in neoplasia. The variability of the effects of cortisone on tumour growth actually reflects the widely divergent effects of cortisone upon tissues. Its administration has been

reported to inhibit the inflammatory reaction, decrease the permeability of capillaries, possibly depress the formation of new connective tissues, suppress mitotic activity, inhibit phagocytosis, exert antihistamine activity, and diminish or prevent immunological responses.[59] It is likely that cortisone does not directly affect the vitality of cancer cells, but the various mechanisms affecting it.

Clinical use of cortisone in treatment of neoplastic diseases produced contradictory results. It is virtually impossible today to trace a common denominator for these findings. In experimental work cortisone was found by some to inhibit the induction of tumours by benzanthracene and methylcholanthrene; others reported that cortisone accelerated tumour production by methylcholanthrene. The dissemination of metastases can be promoted by cortisone administration, even when the primary tumour decreases in size, a result which was called the "paradoxical effect" of cortisone on tumour growth.[35] It was attempted, with some success, to prevent the unfavourable effects of cortisone on neoplasia by administration of anterior pituitary lobe preparations, on the basis that pituitary growth hormone antagonizes the principal effects of cortisone.[36]

The effects of adrenalectomy in experimental animals have been studied in a variety of tumours. With reference to the polyvalent effects of adrenal hormones, it is significant that the growth rate of Walker carcinoma 256, a transplantable, carcinoma-sarcoma of rats, has been found to be considerably diminished (38%) in adrenalectomized animals.[66] The effects on other tumours, such as hepatic tumours induced by azo dyes, are not uniform.

The original observation of Huggins[36] on the effects of castration on prostatic carcinoma formed the basis for modern investigation of the effects of surgical removal of endocrine organs. Later Huggins and Scott[37] suggested combined orchidectomy and adrenalectomy as a logical step to abolish the additional endogenous source of steroid sex hormones. Adrenalectomy has been tried in many centres, and it seems that approximately 40% of patients with breast cancer show remissions lasting for months or years. In the series reported by Stanford Cade,[8] objective improvement was observed in 30% of cases, with a higher rate of subjective improvement. However, as stated by Huggins,[38] the response to adrenalectomy is not uniform and occasionally the growth of a malignant lesion may be accelerated by the procedure. The important question of the etiology of malignancy after adrenalectomy has been asked by Graham,[2] who has demonstrated accessory adrenal tissue in the cœliac region in 32% of autopsies. The presence of such accessory tissue may partly explain the failure of adenalectomy in some cases.

The anterior lobe of the hypophysis as a regulator of endocrine glands and a link with higher nervous centres plays an important though indirect role in neoplastic diseases, being the central relay in preparation of the complex event of hormonal imbalance. Several anterior hypophyseal hormones have been found capable of inducing and maintaining the growth of tumours of target glands; gonadotrophins in the ovaries or testes, thyrotrophic hormone in the thyroid gland and adrenocorticotrophin in the adrenal glands. Growth hormone was shown to favour the occurrence of various tumours in rats, though it did not seem to enhance tumours of mice or the induction of tumours by chemical carcinogens.[22] There is no evidence at present that any particular tumour is "dependent" on growth hormone, which appears to increase the growth rate of tumours only in proportion to the increase in body weight. However, the recent studies of Pearson and his associates indicate that growth hormone may stimulate metastatic growth.[54]

The wide range of metabolic changes controlled or affected by hypophyseal hormones is demonstrated by the physiological effects of hypophysectomy. Here again, as in studies with adrenocortical hormones, many of the experimental results are not in complete agreement and apparently reflect the particular conditions under which the experiment was conducted. Moon, Simpson and Evans[49] have observed inhibition of the formation of sarcomas in hypophysectomized mice which were injected with moderate doses of methylcholanthrene; this inhibitory effect was absent when high doses of the carcinogen were used. The major discussion regarding the effects of hypophysectomy has centred around the question of whether or not the inhibition of tumour growth is based on decreased food intake of hypophysectomized animals. In our studies the caloric intake of the control rats fed 2-acetyl-aminofluorene has been restricted to the levels of intake of hypophysectomized animals; the difference in tumour incidence between these groups remained statistically significant. The experiments of Talalay, Takano and Huggins[67] with tube-fed hypophysectomized rats also indicate that hypophyseal ablation produces its inhibitory effect on tumour growth also in force-fed animals.

The clinical experience with hypophysectomy originated by the series of Luft and Olivecrona[45] seems to warrant use of the procedure in advanced cancer cases of endocrine organs. The largest series reported so far in Canada are those of the Dalhousie University group.[4] The results indicate that hypophysectomy is amazingly successful in bringing about objective remissions in about one-third of patients with breast cancer. Major problems are the selection of cases which will respond favourably to hypophysectomy and the difficulty of radical removal of the pituitary gland.

Hormonal treatment may produce pronounced growth-inhibitory effects, especially in tumours whose etiology is linked to an endocrine background. The original observations of Haddow, Watkinson and Paterson[24] on the influence of syn-

thetic œstrogens upon advanced breast cancer has formed the basis of œstrogen treatment in breast cancer. A recent observation of Segaloff[58] indicates that the beneficial effects of œstrogens might actually be due to depression of pituitary activity.

Testosterone has some definite antagonistic effect upon the role of œstrogens in neoplasia. The inhibition of the promoting effects of œstrogens on mammary cancers by administration of androgens has been demonstrated. It is interesting to note that testosterone has also been reported to cause regression of metastatic thyroid adenocarcinoma.[33] Although biopsies showed the presence of atrophic tumour cells at the site of the metastases, no evidence of progression was observed. This inhibitory effect was observed to be closely related to the adrenocortical function and anabolic activity of the individual.[33]

These examples of the effects of exogenous hormonal therapy on neoplasia demonstrate not only the complexity of the problem, but also the fact that intricate balances rather than individual hormones are of primary importance. The disruption of orderly equilibrium maintained by these mechanisms seems to play a part in the induction of tumours in the hormone-regulated organs. Generally, if a given hormone affects a target tissue, it produces growth and changes in functional activity, and finally influences the differentiation. The suppressive action of some hormones on functional activity of target cells might be related to cancer induction in the sense of Haddow's view[26] that chemical carcinogens act more readily on cells following such depression. Single hormones usually participate in the induction of neoplastic processes accompanied by other factors or conditions (such as species specificity, degree of cellular responsiveness and territorial sensitivity). The division of tumours into dependent and autonomous seems to be both useful and desirable to delineate the known dependency relationships. However, one might question whether, with the steadily increasing number of demonstrated dependencies in relationships, all tumours will be shown eventually to depend at some phase of their development on some growth-regulating hormonal factors.

The development of tumours of endocrine glands following prolonged hormonal imbalance provides an excellent example for the suggestion that any condition of functional imbalance of an organ may be followed by the development of malignant neoplasm.[31] For instance, prolonged functional imbalance imposed upon the liver by choline deficiency first induces fatty metamorphosis, which is followed by cirrhosis and eventually by tumour formation.[31]

The prolonged functional imbalance may be primarily responsible for many tumours occurring in man. The complexity of involvement of endocrine glands in the neoplastic diseases complies with the general rule in endocrinology that complex balances rather than single hormones are responsible. It is to be expected that a physiological regulating mechanism of each particular organ or tissue will be demonstrated as playing an important part in the carcinogenesis of that structure, a concept outlined by Horava[29] as "situations antitumorales". The fact that some effort of the functional unit to counteract any imbalance is always evident offers possibilities in cancer prevention.

NEUROGENIC FACTORS

The information available on the role of neurogenic factors in the etiology of neoplasia is difficult to integrate. Cancer research workers in the late 'twenties were impressed by the possibility of inhibiting tumour growth by a change in neurotrophic control of tissues. Ewing,[14] referring to the experiments of Remond[56] and of Pearce and van Allen,[53] stated: "I regard these observations as of considerable importance in pointing out a possible factor in tissue predisposition to tumour growth." Unfortunately many of the older reports have to be discarded as purely speculative. Of possible significance might be the experimental observations of Mellanby,[48] who concluded that hyperplasia and metaplasia of epithelium in animals kept on a vitamin A-deficient diet is due to loss of neurotrophic control, as evidenced by the development of degenerative changes of medullated nerves in the central and peripheral nervous systems.

For a time the main point of discussion in cancer research was focused on the question of whether or not defective or absent neurotrophic control of tissues is one of the factors predisposing to the formation of malignant tumours. During this period several well-controlled experiments were reported on the subject of denervation and role of blood vessels in the etiology of neoplasia. Although the conclusions drawn frequently exceed the limits of the experiments performed, in quoting them one might follow the motto of Keynes (*Treatise on Probability*) that part of our knowledge is obtained directly and part by argument. Itchikawa, Baum and Kotzareff, and Remond, Bernardbeig and Sandrail[57] subjected rabbits to neurectomy (auricular nerve section) with simultaneous or delayed application of crude tar to the ear and reported an accelerated growth of tumours on the denervated side. Lorin-Epstein and Bodnartschuk[44] performed cervical sympathectomies under similar conditions and reported acceleration of the formation of papillomas and carcinomas. Pearce and van Allen[53] describe a series of experiments including cervical sympathotomy, complete sympathectomy, and superior and inferior sympathectomy, on rabbits bearing transplanted Brown-Pearce sarcoma. Statistically significant differences in the growth of the inoculated tumour were observed between animals whose sympathetic system had undergone operative interference and controls, the distribution of metastases being greatest after complete sympathectomy and sympathotomy. Well-controlled experiments were performed by Tsunoda,[68] who

reported an increased "take" and rate of growth of transplanted tumours of both epithelial and connective tissues after transection of the sciatic nerve. Cervical sympathectomy in rabbits caused increased epithelial growth and invasiveness of tumours produced by tar application.

Cramer[11] entertained the feasibility of segmental loss of sympathetic innervation leading to an increased network of capillary loops around the transplanted tumour, as well as lack of contraction of tumour vessels upon sympathetic stimulation. Shapiro and Warren[60] more recently conducted studies on transplants to the anterior chamber of the eye of Brown-Pearce carcinoma and reported no evidence of rhythmical active motion in the tumour vessels, though response to stimulation was maintained.

In our studies[61] we have attempted to investigate the effects of autonomic blocking agents on experimental carcinogenesis. Two groups of drugs have been considered for use in this investigation.

1. *Ganglionic blocking agents.*—These, as is known, partially block the transmission of both sympathetic and parasympathetic impulses in the autonomic ganglia. Suppression of the sympathetic vasospastic reflex results in peripheral vasodilation, which might have been important in this type of investigation. However, in experimental animals the blocking effects are of short duration and are therefore not suitable for experimental carcinogenesis.

2. *Adrenergic blocking agents.*—The mechanism of inhibition of vasoconstriction by these agents is not perfectly understood; according to newer concepts[51] their action is due to disturbance in equilibrium between the mediator and blocking agent. An alkylamine was added to the diet of male rats kept for 17 weeks on 2-acetyl-aminofluorene administration. In the majority of animals receiving high doses of alkylamine (0.5 mg./g. body weight) tumours appeared earlier. This was particularly well observed in sebaceous-gland carcinomas of the head. The difficulties and limitations in interpretation of the results obtained are fully realized. However, it is of interest to note that Stone[65] observed adrenergic blocking properties in a derivative of fluorene. The relation of the vascular changes produced by adrenergic blocking agents to the absence of the chemical mediator at the neuromuscular junction does not appear to be justified. As stated by Nickerson,[51] the alkylamines do not inactivate epinephrine in tissues, "neither can they prevent a sympathoadrenal discharge by blocking nervous impulses at the ganglionic level".

In his early work on the vascular bed of tumours, Goldmann[19] attempted to establish the hypothesis that human tumours elicit an abundant vascular supply with permanent vasodilation and consequent slowing of the blood stream. Recent observations of Zulch[70] on structure and the formation of blood vessels in glioblastomas appear to be of significance. Zulch[70] found pathological changes in the vessel formation of these tumours, including large lacunar vessels, closed capillary nets with widening of the lumen, glomerular systems and organized vascular systems resembling cavernous formations. He concluded that these changes might in some way be induced by a specific vascular stimulus present in the area of tumour formation, which causes rapid proliferation of new vessels and widening of the vascular lumen. Zulch[70] has also pointed out that brain tumours represent a particularly suitable subject for investigation of endogenous factors, as no exogenous carcinogens, viruses, irradiation effects or chemical substances can be implicated in the causation of these tumours.

The loss of autonomic vasomotor control of a tissue segment could be considered as an etiological factor in the development of neoplasia if some mechanism could be demonstrated to account for permanence, if not irreversibility, of the malignant process. One might postulate that the growth rate of the neoplastic focus depends upon the degree of pre-static hyperæmia, causing concentration of growth-regulating hormonal factors. Simultaneous existence of an ischæmic condition of the surrounding tissues would increase the susceptibility to invasion.

The extent and reversibility of these vascular changes depends, among others, upon the regulating influence of sympathetic vasomotor units and ganglionic transmission. Supposedly this connection is interrupted for some reason and new vasomotor fibres regenerate along the arterioles; the contractibility in a growing vessel is related then to the rate of growth of nerve fibres. The "autonomic balance" of a tissue segment can be maintained by the complex interrelationships with the neighbouring segments. Ray and Console[55] have demonstrated that the return of sympathetic activity after any sympathectomy is not necessarily due to regeneration of nerve fibres, but may be effected through "re-adjustment" by invasion of fibres from an adjacent area. Existence of some pathological process at the ganglionic level, which would impair these processes in a morphogenetic field, would therefore be of importance in determination of extent and permanence of newly formed tissue. Since the nerve cells have no power of regeneration, a ganglionic lesion could be permanent or possibly progressive.

The pathological studies pertinent to these considerations refer to morphological changes in the autonomic ganglia and are difficult to interpret for three reasons: (1) difficulties in establishing a reliable morphological basis; (2) wide range of normal variations; (3) inadequacy of present staining methods of neurogenic elements. Extensive studies in this respect have been conducted by Kuntz.[41] Kuntz studied histological variations in human autonomic ganglion cells obtained at autopsy, using methylene blue and Cajal silver staining techniques. He concluded that heavy

melanotic pigmentation was generally more extensive with progressing age. (The age range of cases studied varied between five weeks and 78 years.) Kuntz[42] can be quoted as stating: "The excessive pigmentation of the autonomic ganglion cells in this group of patients (younger) undoubtedly is associated with the malignant process." No parallel observation in experimental carcinogenesis exists. In our own colony of rats fed 2-acetyl-aminofluorene, no serial studies were performed; however, in several sections of the sympathetic ganglia obtained from rats with malignant tumours hyperpigmentation and necrosis of ganglion cells were evident.

IMMUNOLOGICAL FACTORS

Although the operation of immunological factors in neoplasia has been discussed for a considerable period of time, it is only in recent years that the emphasis in studies of tumour immunology has shifted from diagnostic serology and attempts to induce resistance, to the investigation of immunological aspects of growth. The actual progress in immunobiology of neoplasia has profited by advances made in the basic sciences of genetics and microbiology. The field of immunology of cancer includes such broad subjects as immunogenetics, biophysics and immunochemistry. Many findings in these fields with no apparent relation might eventually prove significant in the immunology of malignant transformation. To give an example, one might quote Pauling's demonstration of the influence of molecular architecture of proteins on their antigenic properties.[52] The biochemical aspect of immune reactions brought immunology closer to the subject of antimetabolites, which forms the basis of Martin's theory of biological antagonists.[46]

On the other hand, two recent clinical developments have contributed significantly to the renewed interest in the immunological factors affecting neoplasia: (1) possibility of an immunological reaction in the verified cases of spontaneous regression of human cancer; (2) homotransplantation of human cancer cells into volunteer recipients.

In some of the cases of spontaneous regression of malignant tumours an immunological type of reaction seems apparent, as in some cases of the well-known series of Stewart.[64] Discussing spontaneous regression, Boyd[5] observed that some of the facts in cases of regression of human cancer "seem to fit the concept of an immunological relationship between tumour and host, activated possibly by some change in the protein complexes of the malignant cells". Upon analyzing the significance of previous treatment in such cases, he drew attention to the fact that in many cases external causes inadequate to eradicate the disease completely, such as incomplete removal, low-dose irradiation, or acute febrile conditions, are frequently encountered in the histories of these patients.[5] In that sense it is possible that good results obtained with radiotherapy of tumour tissue not normally responding to it, or occasional favourable response to a chemotherapeutic agent, might be based not on actual destruction of tumour cells, but on change in the antigenic properties of the tumour. The clinical picture of tumour regression frequently suggests that some alteration occurs in the immunological set-up of the tumour cells and the autologous host.

Southam, Moore and Rhoads[63] recently reported the results of homologous transplantation of tumour cancer cells into subcutaneous tissue of volunteer recipients with and without malignant disease. The survival and quantity of the tumour tissue were increased in cancer patients. In two cancer cases the growth of the implanted grafts was unrestrained as long as the patients survived (six and nine weeks). In one case, metastatic formation in the lymph nodes was observed. After regression of the first transplant, the second implantation of the same cell type was accompanied by increased reaction of the recipient's tissue.[63] Obviously it is too early to draw any conclusions from these experiments. However, if further studies confirm these observations, the practical implications are obvious.

For a non-immunologist, the studies of immunological factors in neoplasia appear to be biased by two conclusions: (1) application of findings obtained with transplanted tumours to all spontaneous tumours. (2) The proposition of immunoreaction as a theory of carcinogenesis. Such a trend is unavoidable; it is also advisable in cancer research to integrate the particular aspects of the problem with the general picture; the critique usually provides the necessary adjustment.

Burnet and Fenner[7] introduced the "self-marker" hypothesis which holds that at a late stage in embryonic life the reticulo-endothelial system becomes capable of recognizing potentially antigenic constituents of the expansible cells of the body as "self-components". Some foreign antigens present at the time may also be recognized as "self-markers" and incapable of acting as antigens on the conditioned animals. In later work Burnet[6] has suggested that cells of many types may be continually liberating "self-markers" into the systemic circulation and that these may exercise a control function.

Medawar and his associates[47] have developed the concept of immunological tolerance as a specific suppression of reactivity induced by exposure to antigenic stimuli before the development of ability of immunological response. These antigens were shown to be of tissue, bacterial or hæmatogenous origin. Immunological tolerance was found to be limited to the antigen in question, thus differing from the so-called immunological paralysis, such as suppression by cortisone or irradiation.

Green[21] has suggested that specific protein complexes characteristic for the tissues in question are modified by action of the carcinogens, the modified complex being capable of self-duplication. According to this theory, the loss of identity proteins (self-

markers) is responsible for the development of adaptation, after initial antibodies production has occurred. The malignant transformation would then be caused by antigenic loss.

Although the search for specific neoplastic antigens continues, present evidence exists only with regard to quantitative differences in the antigenic components of normal and malignant tissues. These were demonstrated by elution techniques, selective absorption studies, metachromatic differential fluorochroming and radioisotope-labelled antibody-antigen systems. As stated by Hauschka,[27] no qualitative antigenic aberrations typical for malignancy have been found so far, and on the whole, the isoantigens of tumour cells are of the same type as those of normal tissues. The findings of Amos, Gorer and Mikulska[1] on the antigenic systems in the mouse lymphomas suggest that malignant leukocytes could be weakly antigenic.

Some of the properties of malignant tissues are more likely than others to be explained by antigenic loss in tumour cells. The ability to metastasize might be linked to the diminution of the isoantigenic differences between the tumour and the autologous host. Immune mechanisms of antigenic loss might also be applied to explain the genetic simplification of cancer cells—the anaplasia. The potentiality to evoke immunological reaction in the host might be expected to decrease with the progression of cancer; however, the increasing simplification of antigenic constitution of tumour cells might occasionally lead to an increased response on the part of the host.

Horava[32] explained the nature of the malignant transformation from the immunological point of view as follows: a cancer-inducing agent disrupts the antigenic mechanism which maintains the tissue integrity. A chromosomal variant of antigenic nature and equal to a somatic mutant occurs and its survival results in appearance of a viable cell equipped with new abnormal potentialities. That tumour tissue might possess tumour-inhibiting properties has been demonstrated by Horava[30] by systemic administration of tumour exudate, derived from the so-called "tumour pouch", to rats bearing transplanted Walker carcinoma of the same types as the tumour producing the exudate. The histological changes observed in the Walker tumour[30] consisted of vasodilation with multiple hæmorrhages, degenerative changes and necrosis of tumour cells. Although several factors might have played a role in this experiment, the inhibitory effect of tumour tissue extracts on the tumour of the same type under the specific conditions of this experiment cannot be doubted.

It has been shown by several investigators that the tumour cells do not exhibit uniform properties, but vary in their response to radiation, drugs, antibodies or viruses. Haushka[28] has further developed these ideas and defines the picture as "neoplastic cell population". According to his diagrammatic representation of important biotypes, a wide range of variant cell types exists within each tumour with a relatively stable equilibrium, resulting from competition between cellular biotypes and "bioselection" by exogenous factors. Hauschka[27] has shown that the variants can be selectively concentrated by propagation in a partially compatible host. Burnet[6] considered the possibility that this selection is confined to cell types not resistant to the immunological destruction, while Hauschka[28] believes that the selection is based on loss of antigenic properties amongst the available variants.

Studies of the immunological factors in neoplasia represent one of the most promising fields in research. As has been mentioned above, the phenomena accompanying spontaneous regression of human tumours are suggestive of an immunological response. It is possible that the reason why we do not observe regression more often in the fully developed cancer is that the capability for regression diminishes with the duration of the process. The fact that cancer is not seen more often may be due to spontaneous regression of minute collections of malignant cells before they become perceptible by diagnostic means. To decipher the immunological factors in tumour susceptibility seems to be one of the most important tasks in cancer research.

CONCLUDING COMMENTS

Investigations of the nature of etiological agents in neoplasia indicate a wide variety and diversity of inducing factors which, under suitable conditions, may induce malignant changes. The term "carcinogen" does not convey the interplay of factors which frequently appear necessary to initiate malignant growth. We have suggested previously (1950) that the development of malignancy depends on the presence of three separate conditions: (1) injury of the cells in question; (2) susceptibility of the tissues; (3) imbalance of hormones regulating growth of the tissues concerned. The non-specificity of factors of etiological significance in tumour induction is probably based on the fact that they affect only one of these conditions and require coincidental presence of factors affecting the other two co-ordinates for induction of cancer. Accordingly, the combination of the etiological factors, rather than the factors themselves, would be specific for induction of neoplasia.

The injury to the cells can be interpreted in the widest possible sense. We have numerous examples of actions of injurious agents in human neoplasia which do not lead to malignancy *per se*, but contribute in some way to its development. Many of the so-called pre-cancerous lesions fall into this class. Chemical carcinogens, such as 2-acetylaminofluorene, produce tumours *per se*, probably because, in addition to the injury, they cause some changes which bring about a breakdown in tissue resistance of the host. It can only be speculated that factors affecting neurotrophic control of morphogenesis and immune response might be of importance in

this breakdown produced by an environmental agent. The extent to which such agents can overcome the defensive host mechanisms determines the incidence of tumours produced. A classical example of a "complete" carcinogenic action is the irradiation effect of radioactive strontium on bone, which in our experience is capable of producing an almost 100% tumour response if an appropriate time-dose relationship is used.

The participation of a third factor—imbalance of growth-regulating substances—appears to be quantitative. Foulds has pointed out that the "progression in malignant characteristics" is a more typical property of neoplasm than the growth itself. It is unlikely that abnormal hormonal conditions play a qualitative role in the induction of neoplasia; nevertheless their presence seems necessary for the expression of some of the properties of malignant tissues. A number of such factors have been demonstrated experimentally to be hormonal in origin, in the ordinary sense of endocrine secretion; they appear to be organ or tissue specific, though obviously any systemic hormonal imbalance is likely to result in focal or local pathophysiological conditions. The future will undoubtedly demonstrate infinitely more complex aspects of hormonal control of growth, including many unsuspected endogenous secretory elements.

To account for the fact that in the majority of common human cancers there is no evidence of action of specific carcinogenic agents, we have previously introduced the term "carcinogenesis without carcinogens", implying a co-ordinate action of neoplastic factors. If cancer is a negative condition, "a manifestation of the breakdown in one or more aspects of the positive control that welds the cells of the body into a single functioning unit", then the investigation of factors which normally control the growth processes seems to be of primary importance. Burnet,[6] from whom this quotation comes, divided the process of control of a collection of living cells into the following components: (1) a pre-existing plan of action; (2) a feed-back mechanism for transmission of information about the state of cells in question; (3) a central control mechanism for regulation of the response to the information transmitted; (4) a reception mechanism in the cells for induction of corrective reactions. We have sufficient evidence to conclude that a number of local and systemic factors participate in maintenance of the processes of control and act at various levels of this scheme.

As far as local factors are concerned, Burnet[6] concluded that the primary requisite for malignant transformation is a loss of the control mediated by physiological contact with adjacent cells. Weiss and Andres[69] have contributed significantly to the understanding of these factors by demonstration that injection of embryonic melanoblastic cells into chick embryos of non-pigmented strain produces proliferation of donor melanoblasts and appearance of melanin granules in the host locations corresponding to the donor site. Moscona[56] has shown that chick-embryo cells, dissociated into separate units by treatment with trypsin, can produce tissue-like associations in tissue culture.

As far as systemic factors are concerned, the participation of hormones in neoplastic processes is sufficiently confirmed, experimentally and clinically. The evidence of participation of factors of immunological and neurotrophic nature is only suggestive. The significance of the systemic factors has been emphasized by generations of surgeons, pathologists and zoologists, the professions which see cancer. To mention only the more recent ones, Dunphy[12] concluded in a review of changing concepts in the surgery of cancer that the traditional notion that cancer is an autonomous growth is untenable in view of "regression of metastases after removal of primary growth, late metastases, great variabilities in the growth rate of various nodules of the same cancer, regression of skin metastases and indisputable evidence of natural defence against cancer." Delarue[13] emphasized the susceptibility and biological growth-control factors in his work on concepts determining the treatment of breast cancer. These clinical observations cannot be disregarded in cancer research. Further investigation of the role of systemic factors in neoplasia and growth control will determine more precisely the factors affecting susceptibility to cancer, which have heretofore been overshadowed by the concept of autonomy of malignant growth. The important studies on cellular constituents and possibly existing chemical differences between normal and cancer cells should not distract us from the major issue of factors controlling growing processes.

The analysis of the presented material suggests that malignant neoplasms develop as a result of interrelated local and systemic processes. In most instances, none of these factors is absolute; all are of only relative etiological importance. On the basis of the concept of progression and the demonstration of the variety of complete and incomplete carcinogenic agents, carcinogenesis emerges as a process depending upon the interaction of carcinogenic, local and systemic factors, a process not completed when the tumour first appears, but one which may continue throughout the course of the disease. The control of this process is effected by several mechanisms. It is possible that among others such systemic factors as an endogenous deficiency or some form of abnormal immune reaction are of etiological significance in the genesis of malignant neoplasms.

SUMMARY

The significance of systemic factors in carcinogenesis is analyzed. The word "systemic" seems appropriate to denote the nature of these factors, implying both the "host" and a particular "system". The most obvious grouping of these factors includes hormonal, neurotrophic and immunological factors. The data available on the participation of hormonal factors in the

neoplastic processes are sufficiently confirmed. Suggestive evidence seems to exist for the action of neurotrophic and immunological factors. The available data are reviewed and our own experimental studies interpreted. It is noted that considerable evidence has accumulated indicating the vast multiplicity and diversity of agents, which under suitable conditions may induce neoplastic changes in tissue. The absence of specific causative agents is stressed in the etiology of the majority of common cancers in man. It is suggested that, with some exceptions, probably none of the factors affecting neoplastic growth is absolute and all are of only relative importance. It is concluded that the process of carcinogenesis is dependent upon the interaction of local and systemic factors, a process not necessarily completed when the tumour first appears, but one which may continue throughout the course of the disease.

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A list of references is not published, for lack of space. Enquiries should be directed to the author.

RÉSUMÉ

L'auteur analyse l'importance des facteurs systémiques dans la carcinogénèse. Le mot *système* semble convenable à décrire la nature de ces facteurs évoquant à la fois l'hôte et l'un de ses systèmes en particulier. Les groupes de facteurs les plus évidents comprennent les facteurs hormonaux, neurotropiques et immunologiques. Les données sur la participation des facteurs hormonaux dans les néoformations ont reçu une confirmation suffisante. Il semble y avoir des preuves suggérant l'existence des facteurs neurotropiques et immunologiques. Les données recueillies à date sont passées en revue et l'auteur interprète ses propres données expérimentales. On doit remarquer que des preuves nombreuses sont accumulées montrant la multiplicité et la diversité des agents, qui dans des conditions propices, peuvent produire des changements néoplastiques dans les tissus. L'auteur souligne l'absence d'agent causateur spécifique dans l'étiologie de la majorité des cancers communs de l'homme. On suggère, qu'à quelques exceptions près, aucun de ces facteurs affectant la croissance néoplastique n'est absolu et tous ne sont que d'importance relative. On conclut donc que le processus de la carcinogénèse dépend de l'interaction de facteurs locaux et systémiques; ce processus n'est pas nécessairement complet lorsque la tumeur paraît au début mais il peut se poursuivre au cours de l'évolution de la maladie.

MITRAL VALVE SURGERY* SIXTY-FIVE CONSECUTIVE CASES TREATED BY MITRAL COMMISSUROTOMY WITH NO OPERATIVE MORTALITY

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MITRAL VALVOTOMY is well established as a valuable surgical procedure, but not all physicians may appreciate how safe the procedure has become.[5, 6, 8] New diagnostic aids, such as left heart catheterization, with or without dye curve studies, are proving to be very valuable in the careful selection of cases.

Before these new aids became available, some complicated cases (i.e., patients with combined aortic and mitral valve disease, or patients with combined stenosis and regurgitation) were subjected to an ineffective operation which resulted in a more stormy postoperative course, high operative mortality and a poor end result. Moreover, some patients who could have been helped were refused operation.

INVESTIGATION

The investigation should include a complete history and careful physical examination. The two most useful additional procedures are taking an electrocardiogram to demonstrate right ventricular hypertrophy or dominance, which so commonly accompanies important mitral stenosis, and fluoroscopy with barium swallow to outline the left atrial enlargement, which is almost always a feature in hæmodynamically important mitral stenosis.

Rheumatic activity must be ruled out by a careful record of the temperature for a few days, together with white blood cell count and erythrocyte sedimentation rate.[1]

Right heart catheterization should be performed where congenital heart disease, such as atrial septal defect or tricuspid stenosis, must be ruled out.

Left heart catheterization* has been a very valuable addition to the armamentarium. It is a certain and safe procedure[2, 3, 9] which provides more information than "wedge" pressure tracings obtained on right heart catheterization ("wedge" pressures are a reflection of left atrial pressure obtained by passing a right heart catheter out into the smallest branches of the pulmonary artery). The specially designed needle is passed through the posterior chest wall under local anæsthesia to enter the left atrium; then a fine nylon catheter is threaded through the needle to pass across the mitral valve into the left ventricle. A pressure gradient across the valve during diastole is the *sine qua non* of mitral stenosis. If aortic valve disease is suspected, pressure in a peripheral artery is recorded simultaneously. The systolic gradient between left ventricle and aorta is then measured, to indicate the severity of aortic stenosis. Mitral or aortic valve stenosis with associated regurgitation is a more complex problem, which cannot be assessed accurately without special techniques, such as the use of dye dilution curves.

*Study supported by the Ontario Heart Foundation and Federal Public Health Grants.

†Department of Surgery, University of Toronto, and Toronto General Hospital; Research Associate, Ontario Heart Foundation.

*Performed on 350 occasions to date with low morbidity and no mortality.

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SELECTION OF PATIENTS

The selection of patients has been well described elsewhere.[1] The ideal candidate should have a clear-cut clinical picture of mitral stenosis, along with increasing disability. The latter may appear as shortness of breath on exertion, or as attacks of pulmonary œdema. There may be associated nocturnal dyspnœa, hæmoptysis or systemic embolism.

Some candidates will have only one or two of these findings. A history of systemic embolism, in the absence of any other disability, is an indication for operation, since amputation of the atrial appendage and an adequate valve opening seem to be effective in the prevention of further embolism.

CONTRAINDICATIONS

General contraindications to operation include age (the oldest patient in this series was 62 years) and other associated conditions such as severe pulmonary dysfunction, infections, or advanced liver disease.

Rheumatic activity should be suspected when there is a recent history of joint pains or malaise. It is remarkable to see how much of such a patient's disability will subside when the myocarditis is brought under control. Only rarely should a patient be operated upon when there is a possibility of rheumatic activity and then only when protected by the anti-inflammatory effect of salicylate or corticosteroid therapy.

Associated mitral regurgitation is suspected when there is a harsh, loud mitral systolic murmur together with clinical, radiographic or electrocardiographic evidence of left ventricular enlargement. Left heart catheterization will help in the selection of cases, so that patients with predominant regurgitation can be deferred for open operation with a pump oxygenator.

Associated aortic valve disease should be carefully assessed. Here, too, there may be left ventricular enlargement. Left heart catheterization may be required to decide whether or not there is aortic stenosis of surgical importance. If there is, combined aortic and mitral commissurotomy should be performed at the same sitting.

Gross cardiac enlargement, advanced pulmonary hypertension, incapacitating arrhythmia, or a heavily calcified valve, also detract from the effectiveness of the operation.

RESULTS AND DISCUSSION

The author operated on 65 consecutive patients, all of whom were so disabled that they fitted into Groups II, III or IV of the classification adopted by the New York Heart Association. Of the early cases, 20 have been followed up from two to five years. Of the remainder, three were lost to follow-up after a couple of months.

Preoperative left heart catheterization was performed in 15 of these patients, because clinically the diagnosis was not certain. Many others avoided a useless operation as a result of left heart catheterization. Digital fracture of the valves was effective in about 90% of cases. An intracardiac knife or dilator was required in the remainder, usually because of the rubbery consistency of the valve. The use of the knife did not appear to increase the postoperative morbidity. It is an absolute necessity in cases in which the rubbery commissures only stretch with finger manipulation, and probably contract back very rapidly to their original dimensions.

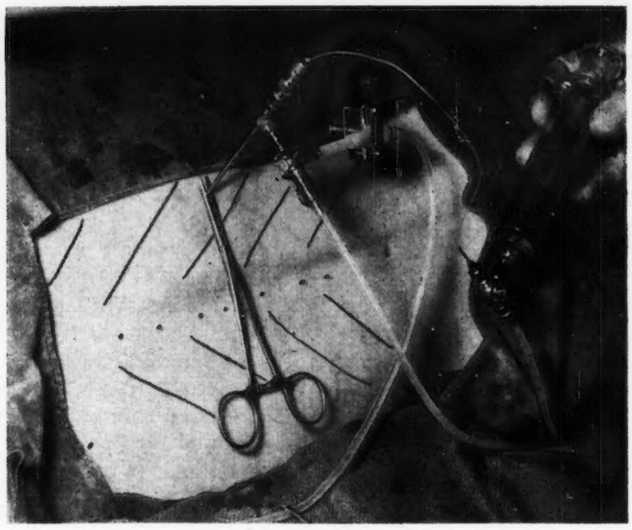

Fig. 1.—Left heart catheterization: Patient lying on left side. Needle inserted into posterior mediastinum at the 8th interspace, and then guided into left atrium fluoroscopically. (Local anæsthesia.)

Calcification

Calcification of the valve was present in 25% of cases, usually demonstrated on fluoroscopy preoperatively, but sometimes found only at the time of operation. The calcification usually involved the aortic cusp as well as the posterior cusp to make them thick, rigid and somewhat immobile, even after the commissures had been split well out to the valve ring. This resulted in a functional obstruction to blood flow in spite of an adequate commissurotomy, and so detracted from the effectiveness of the operation. There were, however, dramatic exceptions to this rule (J.H.). Sometimes the calcification would be limited to the valve ring, or to a single commissure, leaving the cusps unharmed. The development of calcification is a strange, insidious, unpredictable process. One patient (D.P.) had a very effective commissurotomy at which time the cusps were soft, mobile and not calcified. Some two years later he was operated upon for recurrence of stenosis, and was found to have mitral stenosis with heavily calcified cusps.

Thrombus

Thrombus was found in the left atrium of 15 patients (23% of cases). It was usually confined to the atrial appendage, but occasionally extended well into the body of the atrium. In eight patients

(11%) there had been a history of embolism to the brain or limb, some time before operation, but in several of these the atrium was found quite free of thrombus at the time of operation. Serious embolism during operation was minimized in suspected cases by digital pressure applied to the carotid arteries during periods of manipulation of the valve, by a careful flushing out of the appendage before any manipulation or clamping of the atrium was performed, and by isolation and taping of the carotid vessels within the chest in the worst cases. Embolism occurred during operation in two patients. In one the embolus lodged in the left common femoral artery. A retrograde embolectomy was performed from an arteriotomy in the common femoral artery. The patient made a complete recovery with return of all peripheral pulses. Another patient suffered a cerebral embolism during operation and is now slowly recovering from a hemiplegia. Postoperative embolism has not occurred in any patients.

Associated Lesions

Associated mitral regurgitation was found in 15 patients (20%), but was only slight to moderate. Regurgitation was the dominant lesion in only two cases (A.G., R.G.) during the early days of left heart catheterization. In the light of present knowledge and techniques, these two patients would not have come to operation. In one case there was some increase of regurgitation as a result of the operation. There were several cases in which only moderate splitting of the valves was performed, when it appeared that a full splitting would increase the amount of regurgitation.

Subvalvular stenosis was an associated important lesion in five patients (8%). The fixed thickened chordæ tendineæ were split adequately by the finger in these few cases, although it is anticipated that a knife would often be necessary.

Aortic stenosis accompanied the mitral valve lesion in two patients, but was so minimal that valvoplasty was not justified.

Associated tricuspid stenosis was present in two cases. In one patient (K.P.) a satisfactory tricuspid commissurotomy was performed at the same sitting. In the other patient blood transfusions could not be used for religious reasons, so that the tricuspid procedure was deferred to a later date.

Recurrence of Stenosis

Recurrence of stenosis of the mitral valve is a difficult phenomenon to assess.[4] The incidence varies with the adequacy of the first operation,[5] with the amount of thickening and stiffening of the cusps at first operation, and subsequent valve changes. One patient (A.C.) of this series has probably sustained a recurrence of stenosis, although he has not yet been explored. In the other patient (L.R.) death occurred two years after operation after a year of good health. Her valve cusps had become thick and rigid, and were obstructing the flow of blood, in spite of the fact that the commissures had not fused again.

Rheumatic Activity

There must be a constant vigil if rheumatic activity is always to be recognized. One patient (H.G.) had had mitral stenosis for years with very little disability, but then had a rapidly increasing disability which was felt to warrant operation. At exploration of the valve only slight mitral stenosis was found. It was seen in retrospect that her symptoms were all due to the onset of obscure rheumatic activity. Her symptoms subsided only when the activity had been controlled by steroids.

The post-commissurotomy syndrome is an ill-defined complication which can be very disabling to the patient (fever, malaise, pain) and can probably be attributed to several causes. It occurred in six patients (10%) and was controlled by aspirin or prednisone (l-dehydro-cortisone) without much difficulty. Minor forms of it are difficult to recognize, however. It has been suggested that routine postoperative steroid therapy is the best way to wipe out this disabling complication.[7]

TABLE I.—POSTOPERATIVE COMPLICATIONS

Mitral commissurotomy—65 consecutive patients

Cardiac:		
Increased regurgitation	1	
*Ventricular fibrillation	1	
Cardiac tamponade	0	
Post-commissurotomy syndrome	6	(10%)
†Cardiac failure	2	
**Re-stenosis	1-2	(2-3%)
Vascular:		
Cerebral emboli	1	
‡Peripheral artery embolus (common iliac)	1	
Pulmonary emboli (minor)	3	
Deep phlebitis	1	
Pulmonary:		
Severe atelectasis	1	
Hæmothorax	1	
Infections:		
Wound infection	2	
Empyema	0	
Bacterial endocarditis	0	
Miscellaneous:		
Severe incisional pain	1	
Psychosis	0	

*Ventricular fibrillation was easily overcome by electrical defibrillation, with complete recovery of the patient.

†If cardiac failure occurs postoperatively, unrecognized rheumatic activity or an ineffective operation should be suspected.

**Recurrence of stenosis of the mitral valve is probably present in one patient who has not yet been re-explored. Another patient died of her disease two years after operation, but was found to have developed rigid thick cusps, which were obstructing the flow, rather than stenosed commissures.

‡Removed by immediate retrograde embolectomy under local anæsthesia, with rapid recovery of the patient and normal circulation to the limb.

Functional Result

The functional improvement of the patient is always difficult to measure accurately. Attempts to classify their disability preoperatively and postoperatively by standard groupings were misleading.

TABLE II.—FUNCTIONAL RESULT

	No.	*Per cent*
Excellent	18	28%
Good	25	43%
Fair	11	16%
No change	8*	13%

*In two of these patients mitral regurgitation was the dominant lesion, so that the valve was left untouched and will be considered for an open operation on the pump-oxygenator, at a later date.

*Two patients had normal mitral valves with arteriosclerotic heart disease.

*Two patients had active myocarditis as a cause of disability, rather than serious valve disease.

*In one patient the valve could not be explored because of technical difficulties.

An excellent result was obtained in 18 patients (28%) who returned to normal or near normal activities.

A good result with improved ability to climb stairs and do light housework, and with relief of orthopnœa, hæmoptysis, etc., was obtained in 25 cases (43%).

Eleven patients (16%) had a fair result. Here the effectiveness of the operation was limited by associated mitral regurgitation, a calcified rigid cusp, or irreversible pulmonary hypertension which caused persistent right heart failure.

Eight of the early patients (13%) were not helped by their operations because of inaccurate diagnosis or of technical difficulties in splitting the valve (see Table II). The use of the new diagnostic aids would have reduced the size of this group.

Four patients in the series have since died, all between two and four years after operation. Three of these died of progressive rheumatic heart disease and one of a coronary occlusion.

SUMMARY

The author reports on 65 consecutive patients, on whom he performed mitral valvoplasty. The operative findings and complications have been presented. The functional results, with a follow-up of as long as five years, have been reviewed.

ADDENDUM

Since the preparation of this paper, a further seven patients have been operated upon with good immediate results (total, 72 consecutive cases).

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RÉSUMÉ

La valvotomie mitrale est devenue une intervention utile et sûre grâce aux progrès apportés aux méthodes diagnostiques qui permettent un meilleur choix de malades. Le sujet idéal de cette opération doit présenter un tableau clinique bien net de sténose mitrale avec une invalidité croissante qui peut se manifester surtout par de la dyspnée d'effort ou des crises d'œdème pulmonaire, ou encore par de la dyspnée nocturne, de l'hémoptysie ou des embolies périphériques. Les contre-indications comportent une fonction pulmonaire hypothéquée, des infections ou une atteinte hépatique avancée. Elles augmentent aussi avec l'âge. L'efficacité des résultats est compromise par la présence d'une grosse hypertrophie cardiaque, d'une hypertension pulmonaire prononcée, d'une arythmie grave ou d'une valvule grossièrement calcifiée.

L'auteur rapporte ses résultats dans 65 cas à la file, dont 20 furent observés durant deux à cinq ans après l'opération. Quinze d'entre eux subirent un cathétérisme cardiaque et plusieurs autres s'épargnèrent une intervention inutile grâce aux données de cette technique. On observa de la calcification de la valvule dans 25% des cas; elle fut habituellement décelée à la scopie au cours des examens pré-opératoires mais en certaines circonstances, ne fut découverte qu'à l'opération. Il y avait thrombus dans les oreillettes dans 23% des cas. La reformation du rétrécissement valvulaire est difficile à évaluer mais elle semble s'être produite dans un cas opéré deux ans plus tôt. Il faut se garder d'interpréter un regain d'activité de la cardiopathie rhumatismale comme le développement d'une sténose. Les résultats de l'opération furent excellents dans 28% et bons dans 43% des cas.

SOME BLOOD CHANGES DURING EXTRACORPOREAL CIRCULATION IN THE DOG*

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ANY OPERATIVE TEAM ready to offer the services of a heart-lung machine for the correction of cardiac defects must be able, amongst other things, to guarantee the safety of the blood elements.

*This study was subsidized by the Department of National Health and Welfare, and was done in the Department of Research, Laval Hospital. The blood chemistry studies were done by Dr. M. Giroux and staff. The pump oxygenator was under the direction of Dr. J. L. Tremblay.

This is a short report on the changes in some of the blood constituents caused by the extracorporeal circulation. These studies of the blood constituents were carried out as the equipment was being tested, and as the various surgical techniques were being tried out. They cannot be expected to be as normal as they will be in a later, more stabilized series. About half of the animals were perfused by means of a Lillehei-DeWall bubbler, using Sigmamotor pumps. The other half were perfused with a stationary multiscreen oxygenator based on the Gibbon principle and manufactured by the Mark Company. DeBakey pumps were used in conjunction with this screen oxygenator. The machine was primed with dog blood collected at the most a few hours before perfusion. This blood was

collected in siliconized bottles containing from 15 to 20 mg. of heparin. Usually, more than one donor dog was used. Blood groups were not determined, but all blood samples were cross-matched preoperatively. In only one instance was there evidence of agglutination. The blood was kept in a water bath at 37.5° C. until its use.

It is a well-known fact that trauma to blood will release hæmoglobin into the plasma. The amount of hæmoglobin released constitutes a test of good or bad handling, either by the operators or by the machine itself.

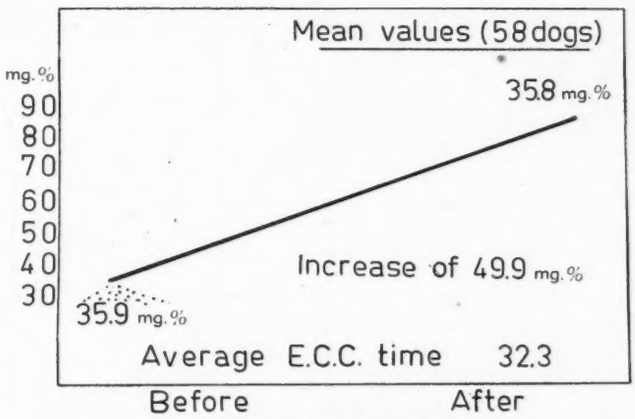

Fig. 1.—Plasma hæmoglobin.

Fig. 1 shows the amount of plasma hæmoglobin before and after circulation. There was an increase of 49.9 mg. % for circulation times averaging 32 minutes and three seconds. The final figure of 85.8% remains acceptable. These are mean values; values were often lower than this, but the occasional erratic case with a high Hb. content brought up the average.

All in all, we were satisfied with the atraumatic handling of the blood. We realize, however, that one mistake in manipulation along the line could lead to near-astronomical figures.

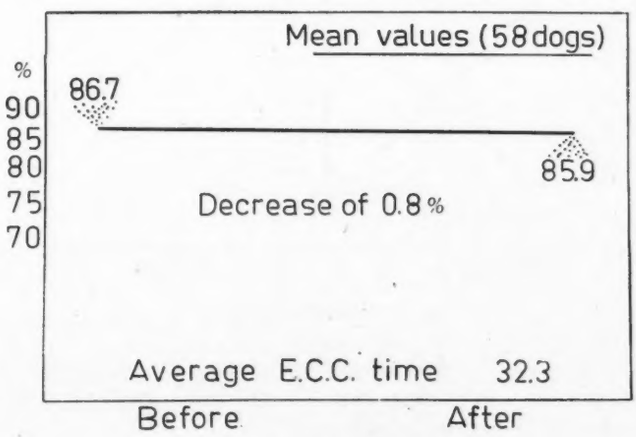

Fig. 2.—Hæmoglobin.

Fig. 2.–The decrease in total hæmoglobin was of the order of 8/10 of 1%. This, we believe, shows how well controlled the blood volume was during various surgical procedures. The chest was aspirated frequently throughout the procedure, and the blood caught in graduated slender burettes for easy determination. All sponges were weighed dry and wet, and the quantity of blood lost in that fashion was calculated. An exact estimation was made every ten minutes. As replacement, citrated blood was used at the beginning of the operation. When heparin was injected, heparinized blood was given. At the end of the perfusion, when protamine was given, citrated blood was again used.

Blood loss could be replaced by adding it to the machine, but we elected to give it directly to the animal. With experience, we made it a rule never to start circulation until all losses had been exactly replaced.

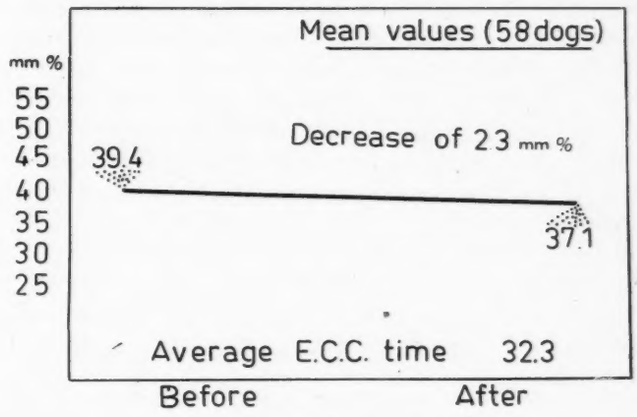

Fig. 3.—Hæmatocrit.

Fig. 3.–The decrease in hæmatocrit value was of the order of 2.3%. This again speaks well for blood replacement. No saline or glucose infusions were given to the animals during the circulation.

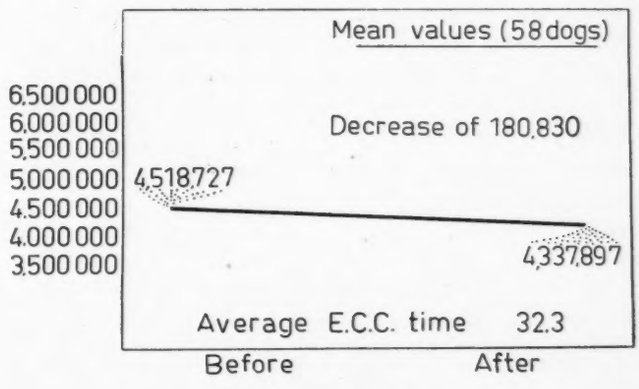

Fig. 4.—Erythrocytes.

Fig. 4.–The decrease in erythrocyte count was of the order of 180,830. This agrees with the data of the two previous charts, showing good blood volume control in so far as such tests can be reliable, when performed in the acute stage, immediately after operation and a run on the artificial heart. Unfortunately, we have no later figures for comparison.

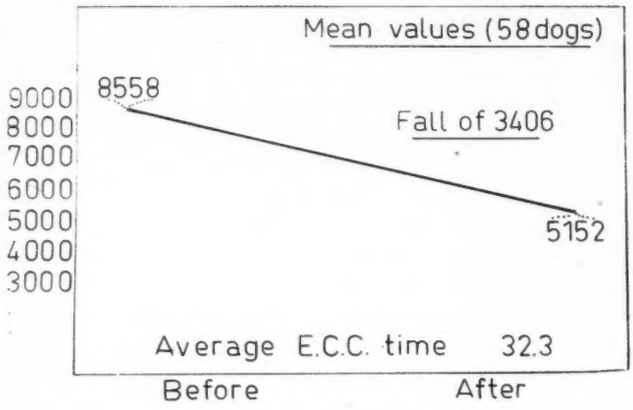

Fig. 5.—Leukocytes.

Fig. 5 shows a drop of 3406 in the leukocyte count. For this we have no definite explanation, but we are inclined to believe that all the white cells have a tendency to adhere to the walls of a plastic oxygenator.

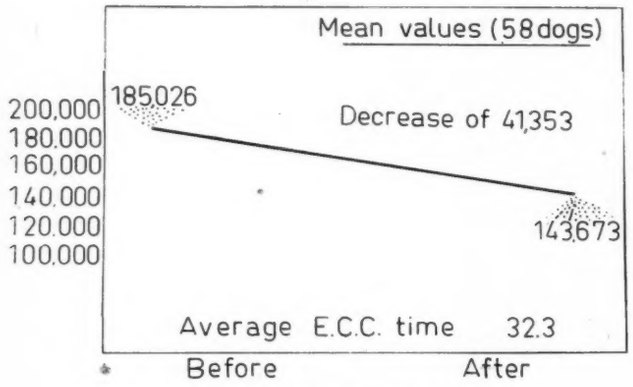

Fig. 6.—Thrombocytes.

Fig. 6 shows a decrease of 41,353 in the thrombocyte count. Since these are amongst the most fragile blood elements, this finding is not surprising. We do not believe, however, that the drop was sufficient to create a bleeding tendency. After extracorporeal circulation, examination of the whitish deposit on the walls of the oxygenator showed this to contain mostly leukocytes, thrombocytes and fibrinogen.

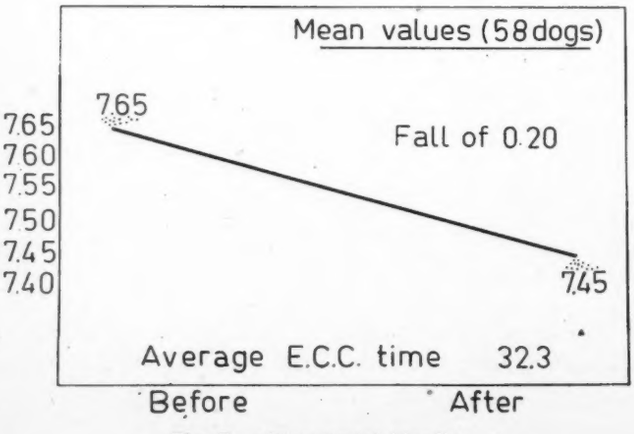

Fig. 7.—pH (arterial blood).

Fig. 7 shows the fall in pH of the arterial blood. The dogs were well oxygenated by a positive pressure machine for varying periods before the start of the extracorporeal circulation. Thus most had reached a state of alkalosis by the time perfusion was begun. With a drop of 0.20 to a mean value of 7.45, we certainly cannot say that our animals were suffering from acidosis at the end of the perfusion.

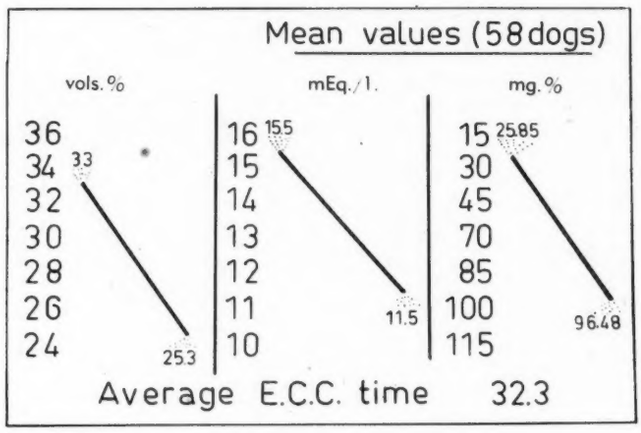

Fig. 8.—CO_2 content.

Fig. 8.—The fall in CO_2 content (by volumes) was of the order of 7.7. This may show a tendency towards metabolic acidosis. Expressed in mEq./l., the fall was of the order of 4 mEq./l. Expressed in mg. %, this fall was of the order of 29.37 mg. %. To correct this tendency to acidosis, postoperatively, the dogs were given sodium bicarbonate in solution intravenously. In a few cases the level of bicarbonate showed a drop at the end of the perfusion.

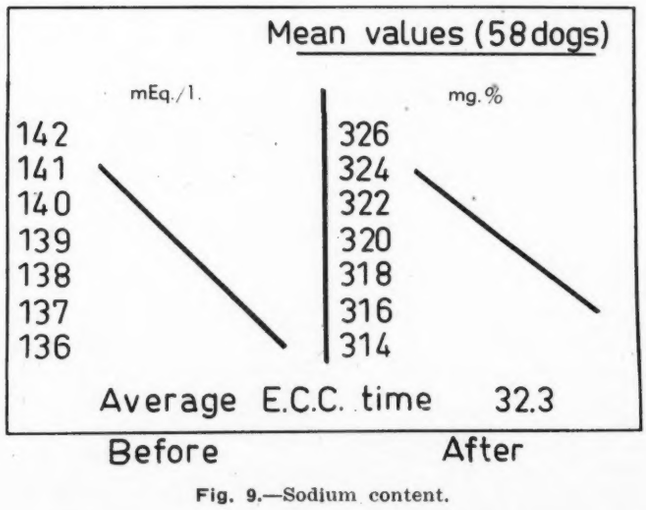

Fig. 9.—Sodium content.

Fig. 9.—The fall in sodium level due to extracorporeal circulation was negligible, and of the order of 5 mEq./l. or 8 mg. %.

Fig. 10.—The chloride content of the blood increased with perfusion. This we believe to be due to the blood transfused to the animal, and to a blood dilution factor in the machine which we shall explain later.

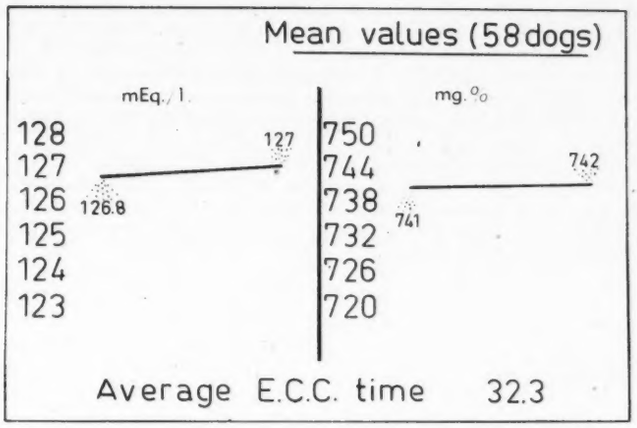

Fig. 10.—Chloride content.

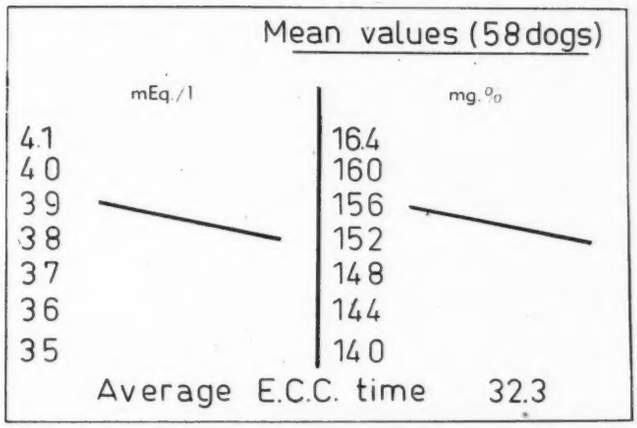

Fig. 11.—Potassium content.

Fig. 11.—The potassium content also showed a negligible fall of 0.1 mEq./l. or 0.4 mg. %.

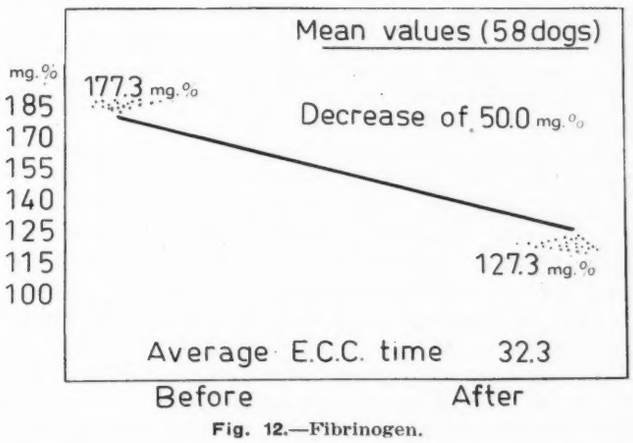

Fig. 12.—Fibrinogen.

Fig. 12.—The fibrinogen level dropped from 177.3 mg. % preoperatively to 127.3 mg. % postoperatively, a decrease of 50.0 mg. %. We would like to prevent this drop. The same cause was probably responsible for the fall in leukocyte and thrombocyte counts.

The following tests were also performed on the blood in the machine just before perfusion: plasma Hb., 65.3 mg. %; Hb., 67.2%; hæmatocrit, 27.2 mm. %; erythrocytes, 3,021,741; leukocytes, 4900; thrombocytes, 114,569; pH, 7.74; CO_2 content, 15.6 vol. %; fibrinogen, 130.6 mg. %. The plasma hæmoglobin level averaged 65.3 mg. %. This decreased with trained personnel, and rose with any addition to the staff, thus showing how important the delicate handling and taking of the blood should be. The decrease in hæmoglobin and hæmatocrit values and erythrocyte, leukocyte and thrombocyte counts is marked and explicable by an identical cause.

In this type of oxygenator, blood enters the oxygenating chamber as saline solution leaves it. Inevitably there is some mixing. As blood is an expensive item, our natural tendency is to save it, and in so doing we retain a certain amount of saline solution, hence the hæmodilution. To prevent this, one would have to lose a bottle or two of blood with the saline drain. At that price, our figures would be closer to normal. However, we hope to do away with saline in the near future. The pH showed a deviation towards alkalosis. This is explained by the recirculation and overoxygenation of the blood in the machine before perfusion, and by the washing out of CO_2. The CO_2 content was diminished both by the hæmodilution and by the recirculation just mentioned. Recently, for this and other reasons, recirculation has been performed with room air, and for the shortest possible time. The fibrinogen level was also lowered, presumably because of the hæmodilution.

These few blood tests, performed during our experimental stage with the heart-lung machine, show that with proper handling of the blood, and with a delicate and precise technique throughout the procedure, one can safeguard the constituents of the blood as well as some of its chemical values.

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RÉSUMÉ

Cinquante-huit chiens subirent différentes interventions au moyen de la circulation extracorporelle. La première moitié du groupe d'animaux fut perfusée au moyen du système à bulles de Lillehei-DeWall. La deuxième moitié au moyen de l'oxygénateur à écrans basé sur les principes de Gibbon.

L'hémoglobine plasmatique augmenta de 49.9 mg. % pour des temps de circulation de 32 minutes en moyenne. Ces chiffres sont d'autant plus acceptables que très souvent ils étaient plus bas, mais quelques erreurs de technique nous donnèrent à l'occasion des chiffres astronomiques. L'hémoglobine totale ne varia pour le même nombre de chiens et pour des périodes de circulation identiques que de 0.8%. Ceci illustre bien le contrôle presque parfait de la volémie.

L'hématocrite ne diminua que de 2.3%. Les globules rouges chutèrent de 180,830. La chute des leucocytes fut beaucoup plus marquée, avec une baisse de 3,406. Les

plaquettes sanguines diminuèrent de 41,353. Cette chute ne semble pas avoir causé de tendances hémorragiques. Toutefois, aprés les séances de circulation extracorporelle, nous trouvons toujours sur la face interne de l'oxygénateur un dépôt blanchâtre, et l'examen d'un prélèvement de cette substance a révélé qu'elle contenait surtout des leucocytes, des thrombocytes et du fibrinogène.

Le pH du sang artériel tomba de 7.65 à 7.45. La chute de CO^2 en volume, fut de l'ordre de 7.7. La chute du contenu en sodium fut négligeable et de l'ordre de 5 mEq./l. Les chlorures augmentèrent légèrement avec les perfusions. Le potassium démontra une légère chute de l'ordre de 0.1 mEq./l. Le fibrinogène tomba de 50 mg. A ce moment dans notre oxygénateur, nous nous servions de sérum salé pour amorcer le circuit. Inévitablement il se produisit un mélange. Conséquemment ceci apportait une hémodilution. Comme nous ne nous servons plus de sérum à l'heure actuelle, nous croyons que le problème de cette dilution sera réglé.

Ces résultats recueillis au cours de nos travaux expérimentaux avec le cœur-poumon artificiel, nous montrent qu'on peut garder le sang en bon état sans trop altérer sa composition chimique, si certaines précautions sont observées durant sa manipulation. J.A.G.

THE EVALUATION OF EMERGENCY GASTRECTOMY FOR HÆMORRHAGE FROM THE UPPER GASTRO-INTESTINAL TRACT*

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THE TREATMENT OF patients with hæmorrhage from peptic ulcer is a subject of controversy. Disagreement revolves principally around the use of emergency gastrectomy (i.e. gastrectomy within 48 hours of hæmorrhage). Should emergency gastrectomy ever be used in the treatment of patients bleeding from the upper gastro-intestinal tract? If so, when, and what are the indications? This study is an attempt to answer these questions.

During the 10-year period 1945-54, 784 patients were admitted to the Toronto Western Hospital with hæmorrhage from the upper gastro-intestinal tract caused by a variety of lesions (Table I). In 692 of these patients the bleeding was from a benign peptic ulcer, and the data obtained from a study of these patients with benign peptic ulcer form the basis of this report. The patients were divided into three groups as follows:

Group I (238 patients) comprised all the patients with hæmorrhage from the upper gastro-intestinal tract from peptic ulcer admitted to the Toronto Western Hospital in the five-year period 1945-49. As only three patients were treated by emergency gastrectomy, treatment was almost wholly conservative.

Group II is made up of 286 patients treated in the five-year period from 1950-54 by the same physicians who had treated Group I. It was expected that these physicians would continue to employ the same conservative method of treatment. However, this expectation did not materialize. Because of the apparent success of emergency gastrectomy a number of physicians adopted this method of treatment. Group II was made up of patients treated both by conservative methods and by emergency gastrectomy, as used in Groups I and III.

TABLE I.—SOURCE OF UPPER GASTRO-INTESTINAL TRACT HÆMORRHAGE OF 784 PATIENTS ADMITTED IN THE 10-YEAR PERIOD 1945 TO 1954

	No. of patients	*Percentage*
Chronic duodenal ulcer	437	55.7
Peptic ulcer (suspected)*	101	12.9
Acute lesion group†	77	9.8
Chronic gastric ulcer	74	9.4
Œsophageal varices	73	9.4
Malignant gastric ulcer	12	1.5
Other (blood dyscrasias, etc.)	7	0.9
Peptic ulcer elsewhere	3	0.4
	784	100.0

*History typical of peptic ulcer but either no ulcer found on roentgenography or roentgenography not done.

†No history of ulcer and either normal roentgenogram or roentgenography not done, other causes of hæmorrhage having been eliminated.

Group III includes 168 patients treated by the author during the five-year period 1950-54. This group differed from the other two groups in (a) the method of investigation, and (b) the use of emergency gastrectomy in selected patients. The operations were performed by the various hospital surgeons, and their cooperation is gratefully acknowledged.

In order to select patients for emergency gastrectomy, it was obviously necessary to know which patients do well and which patients do poorly with conservative treatment. We wanted some rule-of-thumb which would separate these patients. An analysis of the results of treatment used in Group I helped to supply this information. It was apparent that deaths in this group occurred principally in patients over 45 years of age who had gone into shock from massive hæmorrhage. Therefore, according to the age of the patient and to the severity of his hæmorrhage, each patient was classed either as "good risk" or "poor risk" as follows:

(a) Good risk.—These were patients under the age of 45 years with massive hæmorrhage or patients of any age with hæmorrhage not sufficiently severe to produce shock.

(b) Poor risk.—These were patients over the age of 45 years with massive hæmorrhage.

Method of treatment in Group III. Good-risk patients were treated conservatively. Poor-risk patients were treated conservatively unless the bleeding either (a) did not stop within 48 hours or (b) recurred after once stopping. If either of these two events occurred and the cause of bleeding was a known duodenal or gastric ulcer, emergency gastrectomy was performed.

*From the Department of Medicine, the Toronto Western Hospital and the University of Toronto.

In order to carry out this treatment, early diagnosis of the cause of bleeding was essential. To accomplish this, two procedures were used—(a) "no touch" upper gastro-intestinal roentgenography,[1] and (b) the bromsulphalein dye test of liver function.[2] "No touch" roentgenography differs from the usual procedure in that palpation is not used. It was done as soon as shock was counteracted. The bromsulphalein dye test is not altered by hæmorrhage and hepatic anoxia and is therefore particularly useful in ruling out hæmorrhage from œsophageal varices. One exception to this is the patient with Banti's syndrome who may give a normal result to the dye test. However, such a patient is usually young and the question of emergency gastrectomy does not arise.

RESULTS

The three groups were comparable as regards severity of hæmorrhage (Table II), and age and sex. There was a higher percentage of poor-risk patients in Group III, probably on account of the special interest of this study.

TABLE II.—FREQUENCY OF POOR-RISK PATIENTS IN EACH GROUP

	Group I	*Group II*	*Group III*
Good-risk	200	251	139
Poor-risk	38 (15.9%)	35 (12.2%)	29 (17.2%)

The death rates for patients in each of the three groups are shown in detail in Tables III to V and Fig. 1. The overall death rate was reduced from 11.7% in Group I to 4.7% in Group III. Similarly the death rate for good-risk patients was reduced from 4.0% to 1.4% and that for poor-risk patients from 54.0% to 20.6%. Particularly gratifying was the reduction in death rate for poor-risk patients bleeding from gastric ulcer, in whom the death rate decreased from 88.8% to 14.2% (Table V).

TABLE III.—TOTAL NUMBER OF PATIENTS AND PERCENTAGE WHO DIED (PARENTHESES) TABULATED FOR ALL PATIENTS, GOOD-RISK PATIENTS AND POOR-RISK PATIENTS

	Group I	*Group II*	*Group III*
All patients	238 (11.7%)	286 (6.2%)	168 (4.7%)
Good-risk	200 (4.0%)	251 (1.5%)	139 (1.4%)
Poor-risk	38 (54.0%)	35 (40.0%)	29 (20.6%)

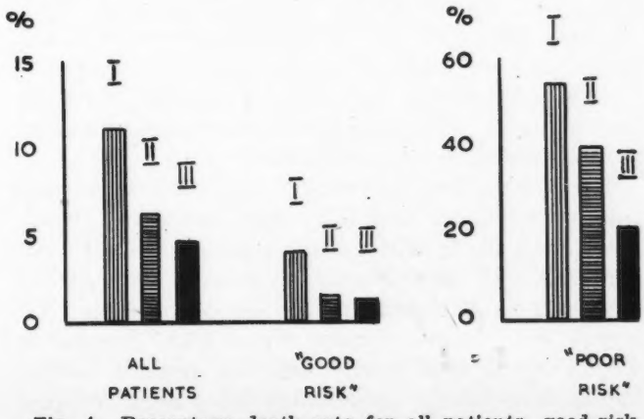

Fig. 1.—Percentage death rate for all patients, good-risk patients and poor-risk patients in study Groups I, II and III.

FACTORS AFFECTING DEATH RATE

As a result of analyzing and comparing the figures of the death rates in the three groups, some important conclusions may be drawn.

Age.—The relationship between the age of the patient and the death rate for Group I and Group III is shown in Fig. 2. In Group I there was a sharp and continuing rise in the death rate after the fifth decade. However, the method of management in Group III reversed this rise.

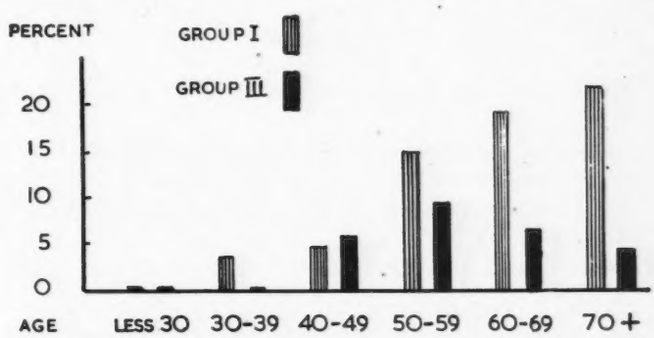

Fig. 2.—Percentage death rate according to age for patients in Group I and Group III.

Sex.—An analysis of all patients in all groups showed no significant difference between the death rate for men (7.5%) and that for women (9.2%).

Cause of hæmorrhage.—The mortality rate from hæmorrhage from chronic gastric ulcer was higher than from any other lesion (Tables IV and V). This was caused by the proximity of lesser curvature ulcers to the right and left gastric arteries, with the danger of erosion into these vessels. The death rates for duodenal ulcer, acute erosion, and peptic ulcer (suspected) were roughly equal and less than for gastric ulcer.

TABLE IV.—TOTAL NUMBER OF PATIENTS AND PERCENTAGE WHO DIED (PARENTHESES) TABULATED FOR GOOD-RISK PATIENTS ACCORDING TO CAUSE OF HÆMORRHAGE

	Group I	*Group II*	*Group III*
Duodenal ulcer	111 (3.6%)	176 (1.7%)	96 (2.0%)
Gastric ulcer	24 (8.3%)	12 (0%)	13 (0%)
Acute lesion	29 (3.4%)	22 (0%)	16 (0%)
Peptic ulcer (suspected)	34 (0%)	41 (2.2%)	14 (0%)
Peptic ulcer elsewhere	2 (0%)	—	—

TABLE V.—TOTAL NUMBER OF PATIENTS AND PERCENTAGE WHO DIED (PARENTHESES) TABULATED FOR POOR-RISK PATIENTS ACCORDING TO CAUSE OF HÆMORRHAGE.

	Group I	*Group II*	*Group III*
Duodenal ulcer	18 (38.3%)	22 (31.8%)	14 (21.4%)
Gastric ulcer	9 (88.8%)	9 (66.6%)	7 (14.2%)
Acute lesion	5 (40.0%)	3 (33.3%)	2 (0%)
Peptic ulcer (suspected)	5 (60.0%)	1 (0%)	6 (33.3%)
Peptic ulcer elsewhere	1 (100%)	—	—

Duration of ulcer history.—There was an inverse relationship between the duration of ulcer symptoms and the mortality rate from bleeding. The death rate for patients with a history of ulcer of less than five years was 10.1%. The death rate for those with a history of ulcer of more than five years was 3.1% (Table VI).

TABLE VI.—DEATH RATES AND DURATION OF ULCER HISTORY

Years	*No. of patients*	*No. died*	*Percentage died*
Less than 5	167	17	10.1
5 to 9	83	3	3.6
10 to 19	103	3	2.9
20+	65	2	3.0

Previous hæmorrhage.—The first hæmorrhage was more dangerous than later hæmorrhages—9.3% mortality rate (42 out of 407) compared with 5.2% (12 out of 230).

Hæmatemesis and melæna.—Hæmorrhage presenting as hæmatemesis (40 deaths in 443, or 9.2%) was more dangerous than hæmorrhage presenting as melæna (13 deaths in 225, or 5.7%).

Recurrent hæmatemesis (after admission).—As might be expected, recurrent hæmorrhage increased the risk of death. Where hæmorrhage did not recur, the death rate was 3.2% as compared with 26.9% in patients with recurrent hæmorrhage.

Severity of the hæmorrhage.—This was the most important factor influencing the death rate, particularly when considered with the age of the patient. Patients with hæmorrhage of insufficient severity to produce shock, or younger patients with massive hæmorrhage (i.e. good-risk patients), had a very favourable prognosis; massive hæmorrhage in older patients (poor-risk patients) was a dangerous event (Table III).

Whole blood transfusions.—The average amount of blood given to each patient transfused was 1604 ml. in Group I, 2043 ml. in Group II and 2204 ml. in Group III. As blood was freely available, the differences in the amounts given were related to the individual preferences of the doctor.

TABLE VII.—INVERSE RELATIONSHIP BETWEEN OPERATIVE RATE AND DEATH RATE FOR POOR-RISK PATIENTS

	Group I	*Group II*	*Group III*
No. of poor-risk patients	38	35	29
Emergency gastrectomy	3 (7.9%)	9 (22.8%)	12 (41.3%)
Death rate	20 (54.0%)	14 (40.0%)	6 (20.6%)

Emergency gastrectomy.—Emergency gastrectomy (gastrectomy within 48 hours of initial or recurrent hæmorrhage) was done in poor-risk patients as follows: Group I—three patients (two deaths); Group II—nine patients (two deaths); Group III—12 patients (two deaths). Four good-risk patients in Group II also had an operation.

Emergency gastrectomy was not used in good-risk patients in Group III, and the improvement in the mortality rate was due to better medical care.

The reduction in death rate among poor-risk patients in Group III comes partly from freer use of blood but principally from the use of emergency gastrectomy in properly selected patients (Table VII).

When all these factors are taken into account, it appears that the major contributions to the improved survival rate of patients in Group III were (a) the method of selection of patients for either conservative treatment or emergency gastrectomy and (b) the increased use of gastrectomy in poor-risk patients.

DISCUSSION

Three methods of treating hæmorrhage from peptic ulcer are being used today: (1) purely conservative, (2) free use of gastrectomy,[3, 4] and (3) conservative therapy combined with emergency gastrectomy in selected patients. The modern trend is toward the third method of treatment. The problem has been critically evaluated by Avery Jones, who writes: "Most clinicians who have had considerable experience in the management of gastric and duodenal hæmorrhage would agree that there is scope for surgery in a selected group of admissions but finality has not yet been reached on the best selection of patients or the best surgical technique to be adopted."[5]

This paper presents (1) a method which has proved satisfactory for the selection of patients for emergency gastrectomy; (2) evidence that when this method was employed to select patients for emergency gastrectomy the survival rate was better than when conservative treatment alone was used.

The next question which arises is whether or not the treatment regimen described in this paper is superior to free use of gastrectomy. In other words, if gastrectomy had been used more often could better results have been obtained? We believe that results would not have been better. Eight patients in Group III died of hæmorrhage. These patients also suffered from one of the following disorders: (1) Laennec's cirrhosis; (2 and 3) malignant hypertension; (4) myocardial infarction with rupture; (5) uncontrollable hæmorrhage and shock (patient aged 85); (6) femoral vein thrombosis and pulmonary embolus; (7) unrecognized perforation of duodenal ulcer, delayed gastrectomy, terminal hæmorrhage; (8) post-gastrectomy streptococcal wound infection and septicæmia.

It is my opinion that none of the first five patients could have been saved by any method of treatment. It is likely that the sixth patient would have survived with more blood, the seventh with earlier diagnosis and treatment of his perforation, the eighth with better asepsis. From these figures, it would seem that there was no patient whose hæmorrhage could conceivably have been stopped by emergency gastrectomy. For this reason it is

believed that the free use of gastrectomy would not have improved the survival rate and perhaps might have lowered it.

A policy of conservative treatment was followed for good-risk patients in Group III. Should this policy be modified? As conservative treatment was also employed in the other two groups (with the exception of four good-risk patients in Group II who had an operation which was considered in retrospect to be unnecessary), the three groups may be combined for analysis.

There were 590 good-risk patients in the three groups, of whom 13 died. Six of these deaths were inevitable because of complicating medical diseases. Seven of these deaths might have been prevented if more blood and, perhaps, surgery had been used. Thus, at best, surgery might have been of value in only seven patients or 1.1% of the good-risk patients. This figure is lower than the expected postoperative death rate from surgery. For this reason the policy of conservative treatment for good-risk patients is believed to be basically sound.

We believe that the failure to demonstrate an ulcer roentgenographically is a contraindication to emergency gastrectomy; however, the suggestion has been made[6,7] that emergency gastrectomy may be a life-saving measure in patients in whom no lesion is seen on the roentgenogram. It is interesting to note that in the three groups there were 139 patients in whom no demonstrable lesion was seen on the "no touch" roentgenogram, and none of these conservatively treated patients died of hæmorrhage. This supports our belief that emergency gastrectomy is not indicated in patients in the presence of a normal "no touch" roentgenogram.

SUMMARY

A series of 692 patients, bleeding from peptic ulcer, has been divided into three groups in order to compare the results of: (a) purely conservative treatment of hæmorrhage with (b) conservative treatment combined with emergency gastrectomy in carefully selected patients.

The method of selection of patients for emergency gastrectomy was as follows:

(a) On admission, each patient was classified as "good risk" or "poor risk", according to his age and the severity of his hæmorrhage. Good-risk patients were those whose hæmorrhage was insufficient to produce shock and those under age 46 years whose hæmorrhage was sufficient to produce shock. Poor-risk patients were those over the age of 45 years with hæmorrhage of sufficient severity to produce shock.

(b) The cause of the bleeding was diagnosed as soon as possible after admission with the help of "no touch" roentgenography and the bromsulphalein dye test of liver function.

(c) Good-risk patients were treated conservatively.

(d) Poor-risk patients were treated conservatively unless the bleeding either continued or recurred after once stopping. In either event they were treated by emergency gastrectomy, provided a duodenal or gastric ulcer had been demonstrated on roentgenography.

The death rate was reduced from 11.7% for patients treated conservatively to 4.7% for patients treated both conservatively and by emergency gastrectomy in selected patients.

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170 St. George St.

RÉSUMÉ

L'auteur a établi une comparaison entre les résultats obtenus dans le traitement de l'hémorragie peptique par des moyens uniquement conservateurs d'une part, et d'autre part, par ces mêmes moyens associés à la gastrectomie d'urgence dans des cas choisis. Ce choix s'établit d'après les données suivantes: le malade doit être âgé de 46 ans ou plus et présenter une hémorragie suffisante à provoquer le choc. Si l'exploration fonctionelle du foie par le B.S.P. est normale, éliminant ainsi la présence d'une cirrhose, le malade passe à la fluoroscopie le plus tôt possible (technique modifiée par supression de la palpation). L'intervention est indiquée si l'hémorragie persiste ou si elle recommence après s'être arrêtée, et pourvu qu'un ulcère peptique ou duodénal ait été trouvé à la radiographie. La mortalité de 11.7% liée à la thérapie uniquement conservatrice fut ainsi abaissée à 4.7% par l'emploi judicieux de la gastrectomie d'urgence.

LIVER BIOPSY TECHNIQUE APPLICABLE TO UNCOOPERATIVE PSYCHOTIC PATIENTS

The usual technique for needle liver biopsy may require modification for uncooperative patients. In studying the effect of chlorpromazine on the liver in uncooperative patients, Foulk *et al.* (*Proc. Staff Meet. Mayo Clin.*, 34: 8, 1959) induced general anæsthesia briefly before the procedure. Fluid and food were withheld for eight hours. Biopsy was performed under sterile conditions with the patient in his own bed, supine with the left arm extended and a sphygmomanometer cuff applied. The antecubital vein was entered with a 20-gauge stainless steel intravenous needle. Pillows were placed beneath the patient's neck to insure a patent airway. Equipment, including airways, endotracheal tubes, a laryngoscope, and a tank of oxygen with a positive pressure mask, was available. The right side of the chest and the flank were cleansed with alcohol and tincture of benzalkonium chloride, and the area was draped with sterile towels. Thiopentone sodium (Pentothal sodium), 4-6 ml. of 2.5% solution, was injected rapidly. The skin was incised in the right 8th-10th intercostal space in the mid-axillary line midway between the upper and lower limits of liver dullness. With a sterile Vim-Silverman needle, transthoracic needle biopsy of the liver was then accomplished during the 20-40 seconds of apnœa produced by rapid administration of the thiopentone sodium.

As soon as an adequate specimen of liver had been obtained, the needle was withdrawn and the patient's respirations were assisted by manual administration of oxygen.

The patient was ambulatory within 5 to 10 minutes and was given breakfast within 30 minutes. The chest and abdomen of the patient were examined routinely one hour and 12 hours after the biopsy.

Needle biopsy was performed in 96 cases in this study with only one minor complication, transient pleural pain; this was no more severe than occasionally occurs after the usual needle biopsy. The entire procedure may be accomplished within 5 to 10 minutes. The procedure is not however, advocated as a routine.

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POWASSAN VIRUS: ISOLATION OF VIRUS FROM A FATAL CASE OF ENCEPHALITIS*

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FOR NEARLY three decades, epidemics of encephalitis due to infection with arthropod-borne viruses have occurred throughout the United States. The virus of eastern equine encephalomyelitis (EEE) caused many cases of encephalitis both in human subjects and horses during the summers of 1938, 1955 and 1956 in Massachusetts.[1, 2] Evidence of activity of EEE virus has also been demonstrated in New Jersey,[3] Georgia[4] and Louisiana[5] by isolation of virus from vector mosquito species *Culiseta melanura* and *Mansonia perturbans*, the presence of antibody to EEE virus in human sera in Louisiana,[6] human infections in Texas,[7] and infections in pheasants in New Jersey[8] and Massachusetts.[2] However, EEE infections are sharply confined to the Atlantic seaboard,[9] only occasional cases occurring as far inland as Wisconsin. Epidemics of encephalitis due to infection with western equine encephalomyelitis (WEE) and St. Louis encephalitis (SLE) viruses occur almost exclusively west of the Mississippi River,[9] although some cases of St. Louis encephalitis have been reported as far east as Kentucky.[10]

In Canada, the only member of the arthropod-borne virus group which hitherto has been encountered regularly in association with human cases of encephalitis is WEE virus. This serotype caused epidemics of human and equine encephalitis in Saskatchewan in 1936 and 1937[11] and a large epidemic in Saskatchewan and Manitoba in 1941.[12] In Ontario, Quebec and the Maritimes, human infections with arthropod-borne viruses are extremely rare, although serological evidence of infection with WEE virus was obtained in one patient in Montreal.[13]

THE POWASSAN CASE

This paper reports the isolation of a virus which shows some serological relationship to Russian spring-summer encephalitis (RSSE) virus, but not SLE, EEE or WEE virus, from the brain of a child who died of encephalitis.

A five-year-old boy who lived at Powassan, Ontario, was admitted to the Hospital for Sick Children, Toronto, on September 17, 1958, during the evening. Three weeks before admission he sustained a swelling over the left eyebrow after a fall from a couch, but he recovered completely after a few days. Twelve hours before admission the child's mother noticed blinking of his left eyelids, and his eyes moved rhythmically to the left. His father noted some tremor and unsteadiness of the boy's left arm. The child complained of dizziness but his gait was normal at this time. This attack subsided after 30 minutes, but a similar attack occurred four hours later.

On admission to hospital the child complained of right-sided headache and he was somewhat drowsy. The temperature was 101° F., blood pressure was 120/60 mm. Hg, and there was no evidence of neck stiffness, nystagmus, or twitching movements. His gait appeared normal, the cranial nerves were normal, and the superficial and deep reflexes were equal and active. The cerebrospinal fluid on admission was under a pressure of 130 mm. water, it had no cells, and the Pandy test showed no increase in protein content. His leukocyte count was 15,900 per c.mm. with a slight neutrophilia.

An electroencephalogram taken on the day after admission showed a moderately diffusely abnormal pattern consistent with any widespread brain disturbance. A skull radiograph showed no bony or space-occupying lesion.

Two days after admission the patient became drowsy, his temperature was 103° F., and neck stiffness was noted for the first time. His gait was slightly ataxic and his right plantar reflex was extensor. The cerebrospinal fluid now contained 150 cells per c.mm., of which 60% were lymphocytes. He became more deeply unconscious as the day progressed, and by the next morning he responded to painful stimuli only. At this time there was intermittent twitching of the right arm, a spastic hemiplegia with increased deep reflexes had developed on the left side, and the plantar reflexes were bilaterally extensor.

Four days after admission he was more deeply comatose and the left-sided hemiplegia persisted. The left plantar reflex was inactive, but the right plantar reflex was extensor. The ankle, knee and abdominal reflexes were inactive. Although the retinal veins of both eyes were tortuous, no papillœdema was noted. An electroencephalogram showed a grossly abnormal pattern suggestive of encephalitis.

During the afternoon of the fourth day after onset, the patient suddenly stopped breathing. He was placed immediately in an artificial respirator. Spontaneous respiration did not recommence, and he died two days later.

At autopsy the brain and meninges appeared normal macroscopically. Histological preparations were made of representative areas of the central nervous system which included the frontal, parietal and occipital cortex; the basal ganglia, pons, medulla and cervical and lumbar areas of the cord. Although numerous staining techniques were employed, all the essential changes were discernible in the routine hæmatoxylin and eosin stain.

An inflammatory process was present in all areas studied. The cord and cerebellum were somewhat less involved than were other areas. The inflammation had two characteristic and predominant components, the one a perivascular infiltration and the other a focal parenchymatous infiltration.

The perivascular infiltration varied in amount. Characteristically, the inflammatory cells were confined to the perivascular space and were composed of lymphocytes and monocytes with a very occasional polymorphonuclear (Fig. 1).

The focal infiltrations showed considerable variation in size. They were situated in the parenchyma, usually the grey matter, and separated from the blood vessels. The collection of cells varied from two dozen in the

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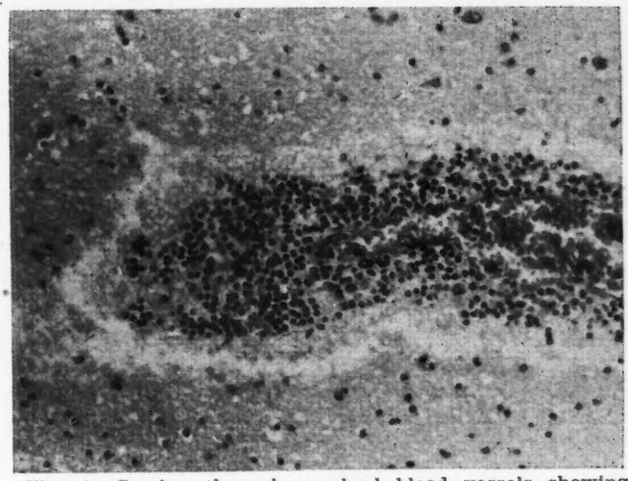

Fig. 1.—Section through cerebral blood vessels showing perivascular cuffing.

plane of the section to many hundreds. Macrophages or microglia predominated, with an occasional polymorphonuclear. In these foci, occasionally, there were degenerating nerve cells with satellite inflammatory cells (the so-called neurophagia (Fig. 2)).

Histologically the lesions were indistinguishable from those described in published accounts of St. Louis,[14] Murray Valley[15] or Japanese B encephalitis.[16]

Portions of brain for virus studies were removed from the left parietal cortex, left basal ganglia and left cerebellum. These were ground in mortars with sufficient 0.85% saline to make a 20% suspension. After centrifugation at 1500 r.p.m. for five minutes, the supernatant was diluted with equal parts of Earle's solution containing lactalbumin hydrolysate 0.5%, yeast extract 0.1%, penicillin 1000 units per ml. and streptomycin 0.5 mg. per ml. This material was inoculated intracerebrally into groups of 9 newborn mice in 0.02 ml. aliquots and into groups of 5 three-week-old mice in 0.03 ml. aliquots.

Newborn mice inoculated with suspensions of basal ganglia and cortex developed signs of acute encephalitis five days after inoculation, and weaned mice inoculated with the same material developed encephalitis on the seventh day. Newborn mice inoculated with suspension of cerebellum developed encephalitis seven days later, but weaned mice inoculated with this material did not become ill during a 14-day observation period. Virus was re-isolated from aliquots of suspensions of basal ganglia and cerebral cortex which were stored at −20° C. for one week.

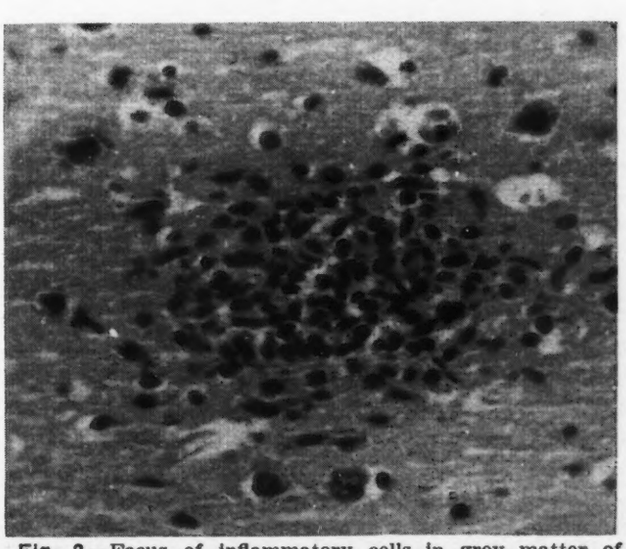

Fig. 2.—Focus of inflammatory cells in grey matter of cerebrum.

The brains of all mice which developed encephalitis were ground with saline containing 10% ox serum to give a 20% suspension. The ox serum was previously heated at 56° C. for 30 minutes. The supernatant following centrifugation at 1500 r.p.m. for five minutes was stored as seed virus in screw-capped vials at −70° C. in a dry ice cabinet. Serial tenfold dilutions of seed virus were made in 10% ox serum saline containing antibiotics, and appropriate dilutions were inoculated intracerebrally into groups of 9 suckling mice between one and five days of age or groups of 5 weaned mice. Seed virus in its second, third or fourth suckling mouse brain passage regularly induced encephalitis five to six days after intracerebral injection of suckling or weaned mice with a 10^{-5} dilution. No cytopathogenic effect was observed after inoculation of monkey kidney tissue cultures with second passage seed virus, and no lesions were observed after inoculation of chick embryos by the chorioallantoic or amniotic routes.

The virus thus isolated from the patient's brain was designated Powassan virus.

Antisera were prepared against Powassan virus and against the viruses of St. Louis encephalitis (SLE), Murray Valley encephalitis (MVE), eastern equine encephalomyelitis (EEE) and western equine encephalomyelitis (WEE) by intraperitoneal inoculation of guinea pigs. These sera were used unheated in neutralization and hæmagglutination inhibition tests, but they were heated at 62° C. for 15 minutes before use in complement fixation tests.

For neutralization tests[17] 0.15 ml. quantities of undiluted serum were mixed with 0.15 ml. quantities of virus calculated to contain 100 mouse LD50 per 0.03 ml. Serum-virus mixtures were inoculated intracerebrally into weaned mice in 0.03 ml. aliquots, or on some occasions 0.02 ml. aliquots were inoculated into suckling mice. "Box type" complement fixation tests using two units of complement were performed in 80-cup plastic hæmagglutination plates (Prestware Ltd., Kingston Road, London S.W.20, England). Hæmagglutination-inhibition tests[18, 19] were also performed in plastic plates, using a 0.25% suspension of erythrocytes of newly hatched chickens. Optimal conditions for hæmagglutination by Powassan virus were pH 6.6 and 4° C. Antigens for use in complement fixation and hæmagglutination inhibition tests were prepared from infected suckling mouse brains by extraction with 2 volumes of saline and centrifugation at 10,000 r.p.m. for one hour. The supernatant fluid was used as antigen.

Antiserum prepared against SLE, MVE, EEE and WEE viruses did not neutralize Powassan virus, and antiserum prepared against Powassan virus did not neutralize heterologous viruses (Table I). Similarly, no cross reactions were demonstrated in complement fixation tests between Powassan virus and four other members of the arthropod-borne group of viruses when optimal concentrations of antigens were used (Table II). However, in hæmagglutination inhibition tests using antisera previously treated with bentonite and chick erythrocytes, the hæmagglutination of chick red cells by 8AD of Powassan virus was inhibited by its homologous antiserum and by antisera against SLE

TABLE I.—POWASSAN VIRUS: NEUTRALIZATION INDICES

Antiserum / *Virus*	*Powassan*	*St. Louis*	*Murray Valley*	*Eastern equine*	*Western equine*
Powassan	100+	0	0	0	0
St. Louis	0*	400	0	0	0
Murray Valley	0	0	1000	0	0
Eastern equine	0	0	0	100+	0
Western equine	0	0	0	0	100

*Signifies neutralization index <10.

TABLE II.—POWASSAN VIRUS: COMPLEMENT FIXATION TITRES

Antiserum / *Antigen*	*Powassan*	*St. Louis*	*Murray Valley*	*Eastern equine*	*Western equine*
Powassan	160	0	0	0	0
St. Louis	0*	160	0	0	0
Murray Valley	0	0	160	0	0
Eastern equine	0	0	0	320	5
Western equine	0	0	0	20	20

*Signifies complement fixation titre <5.

TABLE III.—POWASSAN VIRUS: HÆMAGGLUTINATION INHIBITION TITRES

Antiserum / *Antigen*	*Powassan*	*St. Louis*	*Murray Valley*	*Eastern equine*	*Western equine*
Powassan	640	320	40	0*	0

*Signifies hæmagglutination inhibition titre <10.

and MVE viruses. However, EEE and WEE antisera did not inhibit hæmagglutination by Powassan virus (Table III).

Further tests performed by Dr. J. Casals of the Rockefeller Foundation Virus Laboratories, New York, have shown that Powassan antiserum fixed complement in the presence of RSSE antigen at a titre eight times lower than that for RSSE antiserum, but Powassan antiserum did not fix complement in the presence of SLE antigen. Also, Powassan antiserum inhibited hæmagglutination by 32 AD of RSSE antigen and 4 AD of SLE antigen, both of which viruses belong to Casals' group B, but it did not inhibit hæmagglutination by three other group B antigens and two group A antigens, EEE and WEE.

These results show that Powassan virus is a member of group B of the arthropod-borne viruses.[20] Although it appears to be distinct serologically, it is more closely related to RSSE virus than other group B members.

DISCUSSION

The abrupt onset and rapid downhill course in our case were entirely consistent with that described for severe acute infections with arthropod-borne viruses such as Murray Valley encephalitis[21] or Russian spring-summer encephalitis.[22] The histopathological findings are indistinguishable from those described for encephalitis virus infections.[14-16]

Casals[20] has recently shown that the arthropod-borne viruses may be classified into at least three immunologically distinct groups A, B and C on the basis of their hæmagglutination inhibition reactions. In some instances, cross reactions may also be detected by complement fixation, but neutralization tests[23] have shown that each virus is antigenically distinct. The only members of group A which are found in North America are EEE and WEE viruses, whilst the only group B member known to infect man which has been found up to the present in the temperate zone of North America is SLE virus. MVE virus from Australia is also a member of group B.[24] This appears to be the first occasion on which a virus more closely related to RSSE than to other North American group B members (St. Louis and Bat Salivary Gland viruses) has been isolated from human sources in North America.

The Russian spring-summer (RSS) complex of viruses are distributed extensively throughout Asia, especially Siberia[22] where epidemics of severe encephalitis occur frequently in spring and summer. These viruses caused epidemics in Czechoslovakia in 1948, and in Austria and Slovenia in 1953 and 1954.[25] Ixodid ticks appear to be the principal vectors of the RSS virus complex. From the isolation of a virus resembling RSSE from an Ixodid tick captured in Malaya, Smith[26] showed that this complex extended into equatorial Asia. Study of a large outbreak of Kyasanur forest disease (KFD) during March 1957 by Work and his colleagues[27] has shown that viruses closely related to RSSE caused many human and primate infections in the Kyasanur forest of South India. KFD virus has been isolated repeatedly from *Hæmaphysalis spinigera* adult ticks collected in the forest and from nymphal ticks attached to monkeys, which shows that this species is a likely vector in Kyasanur forest disease. In view of the isolation of a virus related to RSSE from a resident of Northern Ontario, evidence of past infection by this virus will be sought by neutralization, complement fixation or hæmagglutination inhibition tests on human and animal sera, future cases of encephalitis will be studied in detail virologically, and the possible vector role of

ticks and mosquitoes will be investigated by attempts at isolation of virus from wild-caught arthropods.

SUMMARY

A five-year-old boy who lived at Powassan, Ontario, developed acute encephalitis from which he died in September 1958. From three segments of brain which showed histological features typical of infection by an arthropod-borne encephalitis virus, Powassan virus was isolated. This virus behaved as a typical group B member of the arthropod-borne viruses and bore some serological relationship to Russian spring-summer encephalitis virus but it was distinct serologically from previously described arthropod-borne viruses of North America.

We are grateful to Dr. Max Theiler and Dr. Jordi Casals of the Rockefeller Foundation Virus Laboratories, New York, for assistance in characterization of Powassan virus.

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RÉSUMÉ

En septembre 1958 un garçonnet de cinq ans de Powassan (Ontario) mourut d'une encéphalite. On préleva trois échantillons du cerveau portant des lésions typiques d'encéphalite causée par un virus à vecteur d'arthropodes. Le virus Powassan fut isolé de ce tissu. Ce virus se comporte typiquement comme un membre des virus d'arthropodes du groupe B. Il possède quelques traits en commun avec le virus de l'encéphalite russe d'été et de printemps mais il diffère sérologiquement des virus à vecteur d'arthropodes décrits jusqu'à présent en Amérique du Nord.

TWO YEARS' EXPERIENCE WITH STAPES MOBILIZATION*

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WHILE SURGICAL PROCEDURES on the stapes were tried by otologists for otosclerotic deafness as early as 1876, it was not until the development of the antibiotics and the use of magnification in ear surgery that surgical procedures on this small bone became practical. Five years ago when Dr. Rosen first published his results, most otologists were sceptical of its value but now it has become accepted as worth while by leading otologists throughout the world. By frequent exploration of the middle ear under the microscope in the living patient, otologists are getting a much better understanding not only of the pathology of otosclerosis, but also of other abnormalities interfering with the normal function of the ossicles, the round and oval windows, and the drums; these abnormalities were not recognized previously and frequently cannot be differentiated from otosclerosis until the area is examined.

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INDICATIONS FOR SURGERY

Whereas in the fenestration operation improvement can be expected in chronic adhesive otitis media as well as in otosclerosis, obviously mobilization can be successful only in true stapes otosclerosis. An accurate diagnosis is therefore necessary, but, if the history and examination leave one in doubt about the correct diagnosis, an exploratory tympanotomy is justified. If stapes fixation is found, then mobilization may be performed; if not, careful examination and recording of the lesions found should add to our knowledge of middle ear disease. The operation is indicated in less severe losses than fenestration, and these are the cases with the highest chance of improvement. It may be done also in the older patient, or one whose general health would make one hesitant to perform a fenestration. The operation is indicated particularly when there is a mild degree of nerve deafness in addition to the large conductive element. Often in these cases, the hearing can be brought up to the practical level, provided the nerve loss is less than 30 decibels, whereas in the fenestration operation this would be impossible. Mobilization is ideally suited for unilateral cases of otosclerosis, or for bilateral cases where the hearing is still fairly good in one ear.

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CHANGING TECHNIQUES

As in most new operative procedures, modifications develop in the original technique as experience in the procedure grows and there is a corresponding improvement in the results. When Dr. Rosen first started the procedure, he advocated using pressure from the anterior part of the neck of the stapes, backwards. Most of the surgeons using this technique were unable to get better than 30% results because there were too many fractured crura. Then others, such as Goodhill, House and Kos, developed the technique of directing the attack to the process of the incus and the head of the stapes itself, and there was some further improvement in the results, but in some cases this procedure resulted in disarticulation of the incudostapedial joint, particularly where the otosclerotic process was fairly firm and resistant, and there were still many fractured crura.

A further step, which has enabled us to obtain good results in some of the more extensively involved cases, is the wide removal of the posterior tympanic rim, enabling us to get a more exact view of the lesion and direct the attack either to the anterior crus close to the footplate or along the rim of the footplate itself. In some advanced cases with a deeply placed oval window, the crura themselves become fixed to the promontory walls. If the anterior crus alone is involved, good hearing can occasionally be obtained by fracturing the crus and cutting through the footplate just behind the crus, freeing the posterior part of the footplate. If both crura are involved, mobilization is not possible. Dr. Rosen has reported good hearing from fenestrating the footplate in this type of case, but so far this has not been verified by others. I have had no personal experience with the procedure although I watched him do this on a patient where the crura had been removed, with good improvement on the table.

PERSONAL EXPERIENCE

So many papers have been written in recent years on this operation that a complete description of the technique would be repetitious. I will confine myself to some of the factors I have found helpful from my own experience during the past two years.

INCISION

The important point in the incision is to have a very sharp knife. It is helpful to have a small sterile stone present to sharpen the knife before starting, as it gets dulled each time from cutting against the bony canal wall. If the knife is not very sharp, it will tear the skin and leave bands of tissue that make elevation more difficult.

After elevating the drum, I test the hearing. I use an audiometer with a sterile blood pressure cuff for the receiver and cord. I perform only two tests, one before and one after mobilizing, with the drum replaced each time, repeating the last test if required.

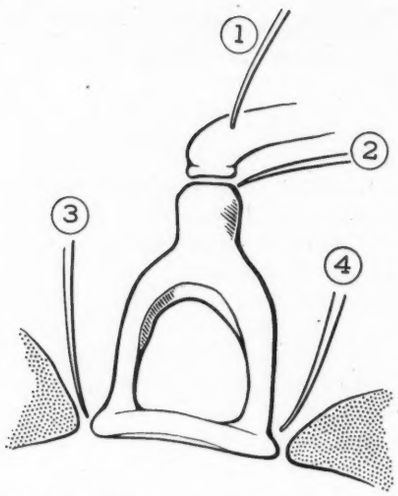

Fig. 1.—Showing areas for application of mobilizers in indirect and direct approach.

Before attempting mobilization, a careful study is made of the anatomy and pathology with the sixteen power magnification. The process of the incus will vary in its position on the head. It may be placed anteriorly, posteriorly or in the middle, and the direction of the force applied will depend on this. Gentle palpation must be used to see whether the inco-stapedial joint is firm or loose (Fig. 1). If it is not firm, mobilization through the incus should not be attempted, or dislocation is likely to occur. The probe must not be too sharp or it may split the incus, or get stuck in it so that the incus is pulled away from the head of the stapes when withdrawing the probe. If the posterior part of the head protrudes behind the incus, it is a useful point to apply pressure, but here again care must be used not to dislocate the joint or split the head.

These methods were used in the first 60 cases, giving about 40% results. After seeing Goodhill's work, I started using the direct approach to the footplate in all cases where gentle indirect pressure failed. This necessitates adequate removal of the posterior tympanic ring from the notch down to the attachment of the chorda tympani, to give a good view of the posterior part of the footplate. I found removal of the tympanic ring difficult at first, but the secret again is to use a sharp curette for which the stone is important, and use the firmly held speculum as a fulcrum for leverage. The curette is rotated in a clockwise direction.

Sometimes the anterior pole of the footplate and the anterior crus can be seen in front of the incus and sometimes it is completely hidden (Fig. 2). If the stapes is tilted a little forward, the anterior crus cannot be seen. In this case, the mobilizer must be placed in position by palpating the anterior promontory wall as it dips down into the window recess, and by following this medially till the edge of the footplate is felt. Pressure is then applied at this point until a slight give is felt. Gentle manipula-

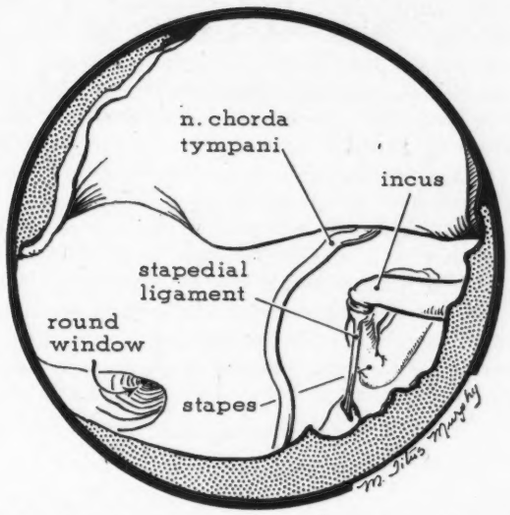

Fig. 2.—View of middle ear as seen through microscope after drum is elevated and part of tympanic rim removed.

tion is again applied to the incus or head to see whether mobilization has been achieved. Success is more apt to result from patient persistence, with gentle pressure alternating between the anterior pole and the joint. If one yields to the temptation to increase the pressure beyond a certain point, fracture of the crura will result, and this point varies with the otosclerotic process and the strength of the crura. Only long experience can teach the right amount in any given case. Sometimes after the anterior pole is free, it is noticed that the posterior part is still fixed. Then manipulation applied to this area will frequently give complete mobility.

RESULTS

Of 133 ears operated on over a period of two years, 90 or 65% have shown satisfactory hearing improvement above the 30 decibel level, while in the last 50 cases, where improved techniques were used, 39 or 78% were successful. This improvement is explained partly by increased experience and partly by the newer techniques used. Of course,

TABLE I.
RESULTS IN 133 CASES

Improved to 30 deb. or better	90	65%
Partial regression	7	8%
Hearing maintained	83	57%

TABLE II.
RESULTS IN LAST 50 CASES

Improved to 30 deb.	39	79%
Partial regression	3	5%
Hearing maintained	36	74%

these are fairly recent cases. The long-term results may be quite different. Several cases in which the stapes appeared to become mobile and which showed improvement on audiometer testing in the operating room did not obtain a good result. I do not know why. There were also a few in which improvement was not apparent on the table, but in which the patient returned in three weeks with a surprisingly good result. These were the exceptions. In most cases, one could tell at once whether or not a satisfactory improvement had been achieved, although there was often a waiting period of three or four weeks before the optimum level was reached. The oldest patient with a good result was 72. The severest loss was 63 decibels. The percentage of good results in cases with losses of over 50 decibels was low in the early cases, but has been better since attacking the footplate directly.

COMPLICATIONS

While this is necessarily an exploratory procedure and the results will depend on the lesions found at operation, one of its great advantages is the minor degree of disability produced. It usually requires only 24 hours of hospitalization and is done under local anæsthesia, with almost no discomfort during the operation and only a moderate degree of discomfort for an hour or so after the local anæsthesia wears off; discomfort can usually be well controlled with one or two injections of meperidine (Demerol). In eight of these cases it was necessary to sever the chorda tympani nerve in order to get adequate exposure, and while the patients are aware of the loss of taste on one side, they do not seem to be disturbed or worried about it, particularly if good hearing results are obtained. In six of the cases a small perforation occurred at the posterior margin of the drum, but all of these healed promptly in a few weeks. One case of middle ear infection was encountered in this series. It occurred two weeks after a successful operation and subsided after intensive antibiotic therapy, leaving a central perforation, but the hearing was still above the 30-decibel level. In only one patient was the hearing made worse, and this to only a mild degree (15 decibels). None of the cases showed any facial weakness and there was no vestibular disturbance of any account. In nearly all successful cases any tinnitus previously present disappeared. Five cases were explored in which a lesion of the ossicles other than otosclerosis was found. I will discuss this later.

DURATION OF RESULTS

As this procedure has been used for only five years, the duration of the improvement is still not determined. Dr. Rosen states that, of the cases he operated on five years ago, only 5% have shown any loss of improvement. Mr. R. S. Venters, of Carlisle, England, who has made a careful follow-up study of his 130 cases, reports regression in 17% of his successful cases, leaving 53% with maintained improvement. These were all done by the indirect method. Kos, who has been performing this procedure for over four years, stated that "despite the increase of immediate postoperative successes, regressions continue to limit the net long-term results."

Of the 90 successful cases, I have had only seven (about 8%) which have shown any loss that I know of. Some of the operations are fairly recent and there are a few patients who live at a distance and on whom I have not made a recent audiogram,

so that the number may be a little higher than this, although I ask all patients to report at once if they notice any drop in hearing. It seems quite likely that this is not a permanent cure, but rather a putting back of the clock for a number of years. It makes one feel rather uncomfortable to know that while the patient is now very happy, the time will probably come when he will be unhappy again. In honesty, all patients should be warned beforehand that they must accept not only the risk of failure, which is now much less than before, but also some risk of early regression. However, if the process starts to re-fix the stapes there is no reason why the procedure cannot be repeated, thus giving a further period of reprieve. If there is a recurrence, it would certainly appear to be a fairly gradual process in most cases. This is not surprising, for after all the initial otosclerotic process seems to take from 20 to 30 years before it causes enough fixation of the stapes to produce a practical hearing loss. Just how long the majority of these cases will be improved for will not be determined until a large number of them have been followed up for a long period. All surgeons doing this work should keep careful operative notes, detailing exactly the lesion found and type of manipulation used, so that we can determine what factors are most conducive to long-term results and vice versa. At the present time, as far as duration of results is concerned, this operation is still on trial.

Other Pathological Findings

In five of the patients some narrowing of the round window was noticed, and in one patient only a very small opening remained, but this did not affect the hearing improvement when the stapes was mobilized. One patient, 30 years old with a severe bilateral conductive deafness, whose mother insisted that she could hear well when younger, was found to have no incus or stapes; we assumed that this condition must have been congenital, in spite of the history of previous hearing. A 12-year-old boy whose early history was vague, and who had a 50% loss with normal bone conduction, was explored and also found to have a congenital absence of stapes. The incus was present, but was tilted posteriorly and there was a short stapedial tendon attached to the incus. Both of these patients should benefit from a fenestration operation, but it should be postponed in the 12-year-old until he reaches a less osteogenic age.

Two middle ears were explored in which careful examination failed to reveal any cause for the conductive deafness, the drum and middle ear being completely normal; this suggests that there may be a completely different cause of conductive deafness from those commonly accepted.

Summary and Comment

The results of two years' experience in stapes mobilization surgery have been presented. A combination of indirect and direct mobilization methods was used. The newer techniques have greatly increased the incidence of immediate postoperative successes, but regressions tend to worsen the long-term results to some extent. The chance of long-term improvement would appear to be between 50 and 60% in skilled hands. While the procedure is relatively easy on the patient, it is by no means a simple operation from the surgeon's point of view. It requires long experience in microscopic surgery and the ability to manipulate the fine microscopic instruments to millimetre precision, in other words, the patience and temperament of a watch-maker. Without the training and temperament, the results are liable to be discouraging. However, in spite of the exacting work and nervous strain the surgeon is amply rewarded by the joy of the patients who hear again after years of being partially cut off from the life around them.

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Résumé

Depuis longtemps déjà, les otologistes ont préconisé la mobilisation de l'étrier dans la surdité par oto-spongiose, mais ce sont l'avènement des antibiotes, l'emploi du microscope et les rapports du Dr Rosen qui l'ont fait accepter dans le monde entier.

On peut s'attendre à une amélioration de l'audition par la fénestration, dans l'otosclérose et dans l'otite moyenne adhésive, mais la mobilisation n'a de chances de succès que dans la sclérose véritable de l'étrier; de là s'impose un diagnostic précis. Cette opération est indiquée dans les pertes moins élevées de l'audition, surtout en présence d'une légère perte par conduction osseuse en plus de la perte plus accentuée par conduction aérienne. Elle peut aussi se pratiquer chez les malades d'un certain âge; elle est idéale dans les cas d'otosclérose unilatérale ou, si bilatérale, lorsque l'audition est encore assez bien conservée dans une oreille.

La technique opératoire a subi plusieurs changements depuis le début (Goodhill, House, Kos, etc.), changements que le Dr Fee explique pour ensuite décrire sa technique et son expérience personnelles, y compris les complications possibles et résultats obtenus. (Ici, il aurait fallu traduire le texte anglais intégralement).

En résumé, l'auteur emploie une combinaison de mobilisation indirecte et directe et dit que les nouvelles techniques ont grandement accru le pourcentage des résultats post-opératoires immédiats qui, à longue échéance, devraient, entre les mains d'un chirurgien habile, se maintenir entre 50 à 60%. Cette mobilisation de l'étrier affecte beaucoup moins le malade que le chirurgien dont elle requiert un long entraînement, un tempérament spécial et beaucoup de patience. J.B.

PAYING FOR YOUR FUN

"Despite the accumulation of evidence pointing the finger at the cigarette as a culprit in lung cancer, it is my opinion that—human nature being what it is—the production of cigarettes (400 billion this year) will continue mounting and the smoker will go puffing merrily on his way following the admonition of a daily radio commercial, 'Don't miss the fun of smoking.' It is my considered opinion that a large percentage of this year's 25,000 lung cancer casualties will be found among those who didn't 'miss the fun of smoking'."—R. C. Oldfield: *Illinois M. J.*, 114: 279, 1958.

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HULA-HOOP SYNDROME

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WITH THE ADVENT of the brightly coloured plastic hula-hoop rings, hooping has spread far and fast over our globe. It has become a popular sport of school children and even adults have not been above joining in exhibitions and contests of endurance. The joy of hooping may not be unalloyed with some hazards in this unusual form of exercise. Since the craze came to Canada, occasional children, both young and old, have presented with unusual aches, pains and other constitutional disturbances which may be a result of excessive hooping round the neck, waist, hips or knees. Sometimes the patient's symptoms are so marked and suggestive of some recognized malady that the child is admitted to hospital. The following five cases illustrate such a consequence. They were observed in the Ottawa General Hospital during the months of October and November 1958.

CASE 1.—B.L., an 11-year-old boy, woke one morning with acute and constant pain in the left loin and the left lumbar region. There was no apparent history of trauma, or gastro-intestinal or urinary disorder, and the temperature and the pulse were normal. On physical examination, he did not look sick and the only positive finding was a moderate degree of tenderness in the left lumbar region. His urine showed no abnormality. He was seen in the emergency department of the hospital by a urologist, a general surgeon and a pædiatrician. The radiologist reported from a flat plate of the abdomen that it was within normal limits. While these services were being provided his pain diminished considerably. On questioning he revealed that the previous evening he had indulged in an unusual amount of hoop whirling round his waist. It seems probable that some exertion or traumatic myositis of his loin muscles on the left side had provoked acute muscular spasm.

CASE 2.—J.H., a 9-year-old girl, was admitted to hospital with pain in the abdomen of three days' duration. It was felt below the costal margin and around the umbilical region. Initially mild, the pain had become more severe and constant on the third day, at which time she also developed pain in the front of the neck when swallowing. She had no fever or apparent contributory history and did not look ill. Examination of the abdomen did not reveal hyperæsthesia, guarding or rigidity, but definite tenderness was elicited below the costal margin and in the umbilical region, particularly on the right side. The neck muscles were slightly tender. Urine, white blood cell count and sedimentation rate were normal. Upon further questioning she owned to excessive hula-hooping about her neck and waist the day before her symptoms commenced. It is thought that this exertion caused interstitial and muscular œdema. The increase in resultant pain and discomfort over three days is not a particularly unusual response to excessive exercise.

CASE 3.—D.L., an 11-year-old girl, was admitted to hospital because of difficulty in walking due to pain. It began five days earlier around both the knees and thighs and was preceded by a sore throat and common cold. The next day, she developed some soreness of the right elbow and later in the neck. She felt tired and slightly feverish. Two days later, she started feeling dizzy with slight discomfort in the right ear, which lasted for six hours. There was no other complaint.

Physical examination revealed normal temperature, pulse, respiration and blood pressure, a slightly congested throat and wax in ears. All the joints appeared normal. However, definite but mild tenderness was elicited in the muscles of the neck and thighs. Other systems were normal. Urine, white blood cell count and erythrocyte sedimentation rate were normal. Questioning revealed that her muscle pain began after prolonged indulgence in hula-hooping.

CASE 4.—C.C., a 7-year-old girl, attended the outpatient clinic because of a moderate and persistent type of pain over the knees, elbows and neck and particularly over the right side of the chest, which had started four days previously. The mother was afraid that the child had rheumatic fever and stated that she had already had a heart murmur and pain in the hand 1½ years ago. There was no history of fever, rash, vomiting, palpitation, dyspnœa, cough or hiccup.

She did not look ill, and her temperature, pulse and respiration were normal. All her joints were apparently normal, and the respiratory system showed no abnormality except for definite mild tenderness over the muscles of the right side of the chest. The heart, though of normal size, revealed a murmur consistent with ventricular septal defect. Her symptoms began after she had participated in a hula-hoop contest. She was sure that she had no pain before that.

CASE 5.—T.S., a 10-year-old girl, attended the outpatient clinic because of an itchy rash round the neck, which had started three days before and followed a mild abdominal pain. At first the rash was erythematous but later it became urticarial and in places was marked with scratches. On the following day, two urticarial wheals appeared over the right side of the face, one over the right forearm and a few small ones over the waistline. There was no fever, vomiting or any other symptom, nor was there any suggestion of inhalation or ingestion of, or contact with, anything unusual to her. Mild upper abdominal tenderness was elicited. Other systems were normal.

Her abdominal pain had begun the day after hooping round the waist, and the itchy rash about the neck on the day she learnt to hoop round the neck. Irritation of a sensitive skin may have provoked the rash and subsequent urticaria, though it is possible that attrition of the skin was combined with sensitivity to the plastic material of the hoop to cause an allergic response. The skin complaint was relieved by an antihistaminic drug.

DISCUSSION

Excessive hooping or going hard at it right away without any previous practice may give rise to symptoms and signs which can be referred to as the

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"hula-hoop syndrome", as the term is descriptive of their common origin.

The cases observed in this hospital did not develop any of the severe complications. They presented with general constitutional symptoms, such as a feeling of fatigue and exhaustion combined with body aches and sometimes mild feverishness. The constant rotatory movements of the head induced by hooping around the neck caused some vertigo and headache, though no patients had nausea or vomiting. The signs and symptoms of muscular origin, forming the major complaint, are induced by overexertion, fatigue, interstitial œdema and spasm of muscles. Myositis or a tear of muscle fibres may occur in severe exertion. The muscular pains can be sufficient to interfere with voluntary movement and occasionally they are acute when there is much spasm and guarding of muscles. In the region of the neck, myalgia can cause not only painful movements of the neck but also pain during deglutition or even torticollis. The pain in the upper limbs was not as common as in the lower, and was felt about the elbows. Pain in the chest was superficially not unlike that of pleurisy, pleurodynia, Coxsackie group B virus affections or intercostal neuralgia. Abdominal pain was felt mainly in the upper abdomen or around the flank, where it was not colicky and could simulate the pain of renal infection, hepatitis, mesenteric adenitis or appendicitis; when colicky it could simulate renal colic. In the lower limbs the myalgia could be confused with affection of the hip or knee joints or give rise to suspicion of rheumatic fever or osteomyelitis. No evidence of derangement of the vertebral column, such as sprain, prolapse of the disc or dislocation, was found. Some excoriation of the skin might be expected where hooping is done to excess about the bare neck or arms, but only one case of allergic reaction due to the irritation of friction or sensitivity to plastic was seen. Subcutaneous hæmorrhages might be expected around any region involved in hooping, in children suffering from bleeding disorders or predisposed to these. Excess of hula-hooping, like other physical exercise, may exacerbate or decompensate any conditions where such physical activity is contraindicated, such as some types of heart disease, rheumatic fever, hepatitis, nephritis, tuberculosis and severe anæmia.

The sequels of hula-hooping may simulate the manifestations of other disease. The object of this paper is to make known such sequels as have been observed, and indicate the necessity nowadays of direct questioning for this form of exertion in order not to be misled or deceived.

SUMMARY

The sequels of hula-hooping may simulate manifestations of other diseases. Five cases are described of pain which came on after the whirling of a hula-hoop around the neck, trunk or limbs. Persistent abdominal, flank and loin pain was seen and in one case it was severe. Pain and stiffness in the chest muscles and thighs were found. In the arms, pain was generally felt at the elbow. Neck muscle pains occurred after hooping about the neck but they were seldom severe. In one case dysphagia occurred and in another urticarial wheals. Dizziness was an occasional concomitant to pain for a day or two after hula-hooping about the neck.

The pain following excessive hula-hooping may last several days, and is similar to that following any other form of unusually severe and prolonged exertion. It is distinguished mainly by the involvement of special groups of muscles used in each variant of the hooping craze. Unless a history of excessive hula-hooping is sought, marked muscular discomfort may suggest other diseases and not the interstitial œdema and stiffness to be expected from excessive muscular exercise of an unusual sort.

ADDENDUM

Since this article was written, some interesting correspondence has appeared in the *British Medical Journal*. Newman (2: 1531, 1958) observed pain at the side of the neck, severe enough to produce torticollis, in children and young adults. He also saw a woman of 68 who presented the classical picture. Nelson (2: 1531, 1958) described a child with moderate neck rigidity, and also attempted to postulate that the waist-level activity may have converted a cystitis into a pyelitis. Beauchamp (1: 51, 1959) observed that a right-leg-stander will perform the action in a clockwise direction, while the left-leg-stander will reverse this procedure. He suggested that "safety lies in insisting on the child being able to perform the exercises equally in both directions". But Brown (1: 369, 1959) thought this "an unattainable counsel of perfection". He wondered why the human species was either right-handed or left-handed. Certain horses and greyhounds are more likely to win when the race course is clockwise or the reverse. In runner beans and shells of snails the spiral is always clockwise from base to apex. It seems justifiable to leave children to hoop in their own natural way.

Vernhet (*Presse méd.*, 67: 563, 1959) reported the case of a 34-year-old woman who developed traumatic rupture of the abdominal rectus muscle after hula-hooping, and presented with an acute abdomen and shock.

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RÉSUMÉ

La vogue du colifichet surnommé Hula-hoop a eu un certain retentissement médical. L'auteur rapporte cinq cas où des douleurs musculaires et de la raideur causées par un effort giratoire prolongé ont simulé le tableau clinique de différents syndromes. Ces inconvénients peuvent durer plusieurs jours et porter à confusion à moins que l'interrogatoire ne mette en évidence cette forme d'activité vaguement apparentée à celle des derviches tourneurs.

FRUITS, SEROTONIN AND CATECHOL AMINES

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SINCE the first report in 1886 by Frankel,[1] up to January 1957, there have been more than 626 recorded cases of phæochromocytoma,[2] 53 of them bilateral.[3] The importance of this tumour resides not only in the fact that it causes one of the curable forms of hypertension, but also in the impetus it has given research in the field of catechol amines. Various pharmacological tests have been devised to facilitate its diagnosis.[4] Recently, emphasis has been placed on chemical determinations of these amines in blood and in urine. Since the original work of Furchgott,[5] easier screening methods for abnormal contents of catechol amines in urine have been developed, the latest by Helmer.[6]

In recent years also there has been a considerable interest in serotonin, whether in relation to carcinoid tumours or to cerebral function. Simple screening tests for the main urinary derivative of serotonin have been devised,[7] as well as more complicated spectro-fluorimetric methods.[8] The problem of establishing normal values of urinary excretion of catechol amines or 5-hydroxyindolacetic acid (5-HIAA) in humans is complex. Until recently only conditions involving metastatic carcinoid tumours were known to elevate the urinary output of 5-HIAA.[9] On the other hand, it is known that various clinical conditions such as stress, muscular exercise, severe thermal burns and operations[10] will raise the excretion of adrenaline, noradrenaline or their metabolites, although rarely within the range found in phæochromocytoma. Recently we have found abnormal values of urinary pressor substances in certain neurological conditions (to be reported elsewhere[11]). Various groups are now investigating abnormal amine metabolism in mental diseases, mainly schizophrenia.

Because of the many variables, it has become necessary to establish careful experimental conditions when measuring urinary catechol amines and 5-HIAA. The previous administration of drugs, the amount of physical exercise and the state of hydration have to be verified. Recently, Anderson and his associates[12] have demonstrated that not only high dietary intake of tryptophan, but also inclusion of bananas in the diet influence the urinary output of 5-HIAA. Subsequently, Waalkes and his associates[13] at Bethesda demonstrated that serotonin, norepinephrine, dopamine and other unidentified amines were present both in the pulp and the peel of bananas. Anderson had shown changes in the urines of four monkeys and of two children in hospital, one of whom had thrombocytopenic purpura, the other phenylpyruvic oligophrenia. These are two disease states characterized by low values of 5-HIAA[14, 15] and in which the metabolism of tryptophan is very likely abnormal.

This investigation was undertaken to study the effect of banana feeding in a normal young adolescent male, engaged in usual activities, upon the measurement of catechol amines and 5-HIAA by screening methods now in use. Other fruits were also added to the diet and investigated for the purpose of comparison.

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METHOD

A 19-year-old male student, in good physical condition and of average mental stability, refrained from participation or attendance in any sport, from sexual intercourse and alcohol. Specific instructions regarding his diet were given daily and the amount and type of all food and drink ingested were recorded. He was allowed to attend classes and do normal amounts of studying. He was not in a period of examination at college. Urine was collected in 24-hour samples continuously and was placed daily in the deep freeze with proper preservative, to be kept until determinations were carried out. The following analyses were made:

1. *5-HIAA:* qualitative, by the method of Sjoerdsma;[7] quantitative, by the method of Udenfriend.[8]
2. *Catechol amines:* by the method of Helmer[6] on a strip of rabbit aorta as modified by Arnold and Rotschild.[16]
3. *Potassium:* by flame photometry.
4. *Creatinine:* by the method of Bonsnes and Taussky.[17]

DIET

After three days of control diet free of fruits, fresh vegetables, salads, juices and alcohol, the subject was given a daily diet consisting only of 11 medium-size bananas, three glasses of fresh milk, five slices of fresh white bread and four scoops of vanilla ice cream for three days. For another three days he was allowed a normal diet as outlined above, plus three medium-size bananas daily. The same control periods before and after the experiment were used with other fruit tested: grapefruit, oranges and a combined diet of all three.

RESULTS

The experiment was divided into two parts. In part one, with various banana feedings, the results were similar to those published by Anderson for 5-HIAA and also demonstrated the presence of pressor substances in the urine (Table I). No variation in 5-HIAA could be produced in part two of the experiment with grapefruit and oranges, amongst the most common table fruits (Table II), but the ingestion of one single banana produced measurable changes.

DISCUSSION

Creatinine excretion was fairly stable and the urinary volume varied little from day to day.

TABLE I.—EXPERIMENT NO. 1—RESULTS

Day	Type diet	5-HIAA mg./day	Pressor substance µg./day	Sjoerdsma qualitative	Potassium urine mEq./day
1.	Normal	4.9	0	neg.	—
2.	Normal	3.7	0	neg.	76
3.	Normal	3.0	0	neg.	69
4.	High banana	43.3	1000	pos.	82.5
5.	High banana	40.6	1050	pos.	—
6.	High banana	37.0	750	pos.	—
7.	Low banana	12.7	475	neg.	—
8.	Low banana	11.3	375	neg.	115
9.	Normal	3.7	0	neg.	—
10.	Normal	1.9	0	neg.	—

The caloric intake was high but within normal range for a growing adolescent. Variations in the diet were within an expected range, and did not correspond to the findings in urine. On the other hand, potassium intake was markedly increased during the days of special diet, mainly because fruits have a high content of potassium.

With banana feedings, it may be concluded that the total amount of serotonin ingested from that source is excreted during the same 24-hour period. This fact will minimize the possibility that high urinary values of serotonin from this dietary source will be mistaken for a pathological state. The results are within the expected and calculated limits if one uses the average figure of 3.5 mg. of serotonin per medium-size banana, as calculated by Waalkes.[13] Thus, there does not seem to be any storage of the serotonin ingested through bananas. It is possible, of course, that the banana serotonin is metabolized and replaces existing serotonin in the body. Only radioisotope studies will clarify this point. The ability of iproniazid to block the excretion of 5-HIAA after banana feeding as demonstrated by Anderson[12] may be an indication that oxidative de-amination of the ingested product does occur under these experimental conditions. It is doubtful, however, whether ingestion of large quantities of bananas causes biological problems within the human body through the effect of serotonin either on the gastro-intestinal system or the brain. Many therapeutic uses have been claimed[18] for bananas, mainly in cœliac disease, peptic ulcer and constipation, but the results of this study would indicate that the mechanism involved is not through the action of serotonin.

It is interesting to note that the qualitative test for 5-HIAA was positive on the days of high banana intake. It is usually negative below a level of 20 mg. of 5-HIAA in urine in our laboratory. For a patient like the one under study, whose mean normal excretion over 12 days is 3.7 mg./day, it would require at least 5 or 6 bananas daily to cause a false positive reaction. But it seems reasonable that in patients whose normal is in the upper limits (9-10 mg./day) or who suffer from diseases known to elevate the 5-HIAA excretion,[19] such as gout, ordinary banana consumption could cause false positive reactions in the qualitative test.

TABLE II.—EXPERIMENT NO. 2—RESULTS

Day	Type diet	5-HIAA mg./day	Sjoerdsma qualitative	Potassium urine mEq./day
11.	Normal	4.5	neg.	93.5
12.	Normal	4.1	neg.	—
13.	Grapefruit	3.4	neg.	72.0
14.	Grapefruit	3.8	neg.	—
15.	Normal	5.2	neg.	—
16.	Normal	3.9	neg.	—
17.	Oranges (juice)	4.4	neg.	—
18.	Oranges	5.2	neg.	105.0
19.	Normal	3.8	neg.	—
20.	Normal	3.1	neg.	—
21.	Combined	6.6	neg.	—
22.	Normal	2.5	neg.	—

The same remarks apply to the abnormal findings of pressor substances in the urine of this subject. Unfortunately, with the test used we cannot calculate the turnover or determine which amine is involved. The rabbit aorta response is a fairly satisfactory screening method for phæochromocytoma, because it will certainly indicate the presence of abnormal pressor substances in the urine and, when properly used, give a semi-quantitative estimation of their concentrations. The limits accepted as normal must be much higher than the values cited by chemical determinations.[6, 16] But even with these restrictions, the values found in this experiment are well above normal and within the range for patients with phæochromocytoma and other conditions giving high readings.[11] Bananas thus cause false positive results, at least with this specific method of testing.

The nature of the pressor substance was not determined. It is known[16] that 5-HIAA, noradrenaline, adrenaline, dopamine and other catechols can cause a contraction of the muscle strip, so it is impossible to establish to what extent each contributed to the rise. We only know that the contraction was cancelled out by the addition of phentolamine (Regitine) to the bath in the muscle perfusion chamber, as recommended by Helmer.[6] This would tend to rule out other substances such as kallidin.* It must also be noted that ingestion of bananas or other fruits did not cause changes in the blood pressure or pulse in our subject.

Since completion of this manuscript, we have tested three more subjects on a high banana diet and have had similar results as far as the rabbit aorta test is concerned. Chromatographic studies have shown that at least part of the contraction obtained is due to an increased amount of noradrenaline in the urine. We have already seen that serotonin derivatives could account also for part of the contraction. Meanwhile Puente-Duany[20] had studied the effect of banana ingestion on urinary excretion of 5-hydroxyindole compounds in 10 normal adults. His results agree with ours, except for much higher control values. He does not mention the effect of banana feeding on catechol amine excretion, as measured by the usual biological tests.

*A depressor polypeptide formed by the action of kallikrein, an enzyme found in the urine, on α-2 globulins of the plasma.

It is of interest that grapefruit and oranges, the most common table fruits with bananas, do not cause measurable changes in the excretion of 5-HIAA.

SUMMARY

When bananas were fed to a normal male adolescent, the amounts of 5-HIAA found in the urine corresponded to the calculated amounts of serotonin fed during the same day. It is suggested that an abnormal intake of bananas has no direct physiological effect due to serotonin on the normal human body.

Ingestion of grapefruit and oranges did not modify the excretion of 5-HIAA in the urine.

Ingestion of bananas was sufficient to cause false positive reactions in the qualitative test of Sjoerdsma for 5-HIAA in the urine, and in determination of urinary pressor substances based on contraction of rabbit aorta. This false positive reaction will very seldom cause an erroneous diagnosis of carcinoid tumours or phæochromocytoma, because few physicians depend on only one laboratory test, or on a single determination; but it can be of great importance in the interpretation of results in certain fields of research such as mental disease.

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RÉSUMÉ

Un sujet normal nourri uniquement de bananes excrète dans l'urine une quantité d'acide 5-hydroxyindol-acétique à peu près égale à la quantité mesurée de sérotonine contenue dans les bananes. Nous croyons que l'ingestion de quantités anormales de bananes ne produit aucun effet physiologique attribuable directement à la sérotonine. L'ingestion de pamplemousses et d'oranges n'a aucun effet sur l'excrétion d'acide 5-hydroxyindol-acétique dans l'urine.

L'ingestion de bananes fut cependant suffisante pour causer de faux positifs dans la réaction de Sjoerdsma (servant à déterminer les métabolites de la sérotonine dans les urines) et dans la détermination des substances vasopressives urinaires par la contraction de l'aorte de lapin. Nous ne croyons pas que ces faux positifs puissent causer de mauvais diagnostics de tumeurs carcinoïdes ou de phéochromocytomes, si le médecin prend soin de ne pas se fier complètement à un seul résultat de laboratoire. Cependant cette observation peut être d'importance capitale en recherche, surtout dans l'étude des catéchol amines dans les maladies mentales. A.B.

A NEW COLONIC EVACUANT, Bisacodyl (Dulcolax)* CLINICAL TRIAL IN POSTOPERATIVE CASES

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EVERY SURGEON has looked forward to finding in his therapeutic armamentarium a safe and effective product, easy and rapid of administration, capable of producing the first postoperative intestinal evacuation for his patient. Till now, the safest method has been by enema. Besides the fact that it is not totally harmless, the enema is a tiring experience, is far from pleasant for the patient, and is also a tedious task for the hospital personnel.

Therefore, the launching of a new compound on the Canadian market was greeted with interest since, according to clinical investigators[1-4, 6, 7] it was claimed that it could replace almost entirely the use of enemas and of other laxatives, for the preparation of patients either for x-ray examinations or abdominal operations, as well as for postoperative intestinal evacuation.[5]

This product, bisacodyl or bis-(*p*-acetoxyphenyl)-2-pyridylmethane, commercially known as Dulcolax, was clinically investigated as a preoperative and postoperative laxative in our Department of Surgery. However, this study outlines only the results obtained on postoperative administration, since other authors have reported the effectiveness of this drug as a laxative in ordinary conditions of life, and we do not believe that one individual differs very much from another in this respect before an operation.

Bisacodyl (Dulcolax) is colourless and tasteless. It acts by contact with the colonic mucosa, producing a reflex stimulation of peristalsis. Experi-

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mental studies have demonstrated that it is not absorbed; consequently it is not present in the milk of nursing mothers.[3] It is not toxic, whether given in massive doses or after prolonged use. It is presented in two forms, tablets and suppositories. The tablets are of 5 mg. whereas the suppositories contain 10 mg. of the active ingredient.

MATERIAL

Bisacodyl (Dulcolax) was administered to 74 patients (46 females and 28 males) after a surgical operation. The patients were not selected but were taken at random as regards sex, age, and surgical operation.

Age

Table I indicates the age of patients included in the study. The youngest was 2 years of age and the eldest 79.

TABLE I.—AGE OF SUBJECTS

0 - 9	5
10 - 19	18
20 - 29	10
30 - 39	11
40 - 49	14
50 - 59	7
60 - 69	6
70 - 79	3
Total	74

Surgical Cases

The number and type of operations performed are illustrated in Table II. Only in six cases was no peritoneal opening made.

TABLE II.—SURGICAL CASES

Appendectomy	27
Laparotomy for intestinal obstruction, intestinal perforation, perforated ulcus, adhesiotomy	19
Cholecystectomy	7
Hysterectomy	5
Herniotomy	4
Salpingo-ovariectomy for ovarian cyst	4
Hæmorrhoidectomy	4
Gastrectomy	2
Transposition of the cord	1
Hydrocele	1
Total	74

METHOD OF ADMINISTRATION

The two forms of administration, by tablets and suppositories, were used as follows: the tablets alone were administered to 19 patients (15 females and 4 males) and the suppositories alone were given in 47 cases, divided between 26 females and 21 males. For eight cases (5 females and 3 males) the two forms of administration were used. As eight patients were given both tablets and suppositories combined, the tablets were administered to a total of 27 patients and the suppositories to a total of 55 patients.

No major side reactions were encountered with either form of administration.

RESULTS

In Table III, we indicate the day of administration, the number of patients for each day, and the result in each case. The tablets were preferably given at night, thereby allowing the intestinal evacuation to occur the next morning only, and preventing the patient's sleep from disturbance by a nocturnal evacuation.

TABLE III.—POSTOPERATIVE DAY OF ADMINISTRATION

	Patients	*P.O. day*	*Effective*	*Not effective*	*% of effectiveness*
Tablets	17	2nd	14	3	82.3%
	9	3rd	6	3	66.6%
	1	4th	1	0	100%
Total	27		21	6	77.7%
	Patients	*Day*	*Effective*	*Not effective*	*% of effectiveness*
Suppositories	10	2nd	7	3	70%
	33	3rd	29	4	87.8%
	12	4th	12	0	100%
Total	55		48	7	87.2%

The tables establish that the most opportune time to administer the tablets is in the evening of the second day after the operation, whereas the suppositories seem to be more effective on the third day. Since we aim for an evacuation as soon as possible after operation, we believe that delaying until the fourth day would be too long.

Tablets

Used alone, the tablets were effective in 18 cases out of 19. The only failure noted was in a hæmorrhoidectomy case, in which the male patient had been given two tablets.

In the eight cases where suppositories and tablets were combined, the result was as follows: in five instances, the tablets were ineffective and we resorted successfully to suppositories the next morning. In the three other cases where the suppositories had been ineffective, the tablets gave good results.

Three tablets were given in 7 cases, two tablets in 19 cases and one tablet in one case. In general, the tablets produced the desired action eight to ten hours after administration.

Suppositories

Used alone, the suppositories were effective in 43 cases out of 47. We noted two failures in women to whom one suppository had been administered, and two in men given two suppositories. The women had undergone appendectomy and ovariectomy respectively, the men gastrectomy and herniotomy. As previously mentioned, in the combined administration of suppositories and tablets, the suppositories contributed to the success of the tablets in five instances, and reciprocally the tablets helped the action of the suppositories in three cases.

Two suppositories were administered 29 times, and one suppository was given 26 times. In general,

the action followed administration within 60 minutes, and in almost two-thirds of the cases it was achieved between 15 and 45 minutes.

Degree of Effectiveness

The effectiveness of either tablets or suppositories was obviously not uniform in all cases. Of the 69 cases where bisacodyl proved its effectiveness, 54 had excellent results; in the 15 other cases, the results, if not excellent, are nevertheless not to be disregarded since no other laxative was necessary.

In summary, the absolute effectiveness rate (69 out of 74) is 93.2%, with 73% excellent results. In the five cases considered as failures, we most probably would have obtained results had we combined the suppositories with tablets or vice versa. The suppositories, we believe, were slightly more effective than the tablets, as illustrated in Table III. Two tablets have seemed just as effective as three tablets, whereas the administration of only one suppository was nearly as effective as two suppositories.

Finally, the action of bisacodyl seems obviously the same in both sexes.

Opiates

Our attention was not centred on the consistency of stools obtained. The important factor for us was not to induce a formed or loose stool, but to re-establish function of the intestine. The possible role played in the action of bisacodyl by preoperative and postoperative sedatives was considered. Morphine, Sedol and meperidine were the sedatives prescribed for our patients before and after operation. The effect of the sedatives on the action of bisacodyl was non-existent, apart from maybe a slight delay in the action of the suppositories as well as the tablets, compared to the action observed in the same patients before operation.

Of the five cases where bisacodyl failed to produce an action, only one was in the group of those given a high dose of sedative, and this case (of gastrectomy) was one of long-standing chronic constipation. Two failures were registered in cases after slight sedation; the other two belonged to the group given an average dose of sedative.

It is therefore not proven that opiates interfere with the action of bisacodyl; in our opinion, an individual factor is involved, and this factor exerts its influence as well after operation. It is a fact that some persons with sensitive bowels react violently to the slightest laxative, whereas others respond only to high doses of powerful laxatives.

SUMMARY

Bisacodyl (Dulcolax), a contact laxative, was administered to 74 patients to induce the first postoperative intestinal evacuation. Whether in tablet or suppository form, it was effective in 69 of these cases. No side reactions were encountered.

The patient's age and type of operation performed are indicated. Postoperative sedation seems to have only a very slight influence on the action of bisacodyl. The simplified and easy method of administration makes it an ideal laxative when surgery is indicated.

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RÉSUMÉ

Un laxatif de contact, bisacodyl (Dulcolax, *marque déposée*), fut administré à 74 malades afin de provoquer la première évacuation intestinale post-opératoire. Ce médicament se montra efficace chez 69 d'entre eux. La présentation est sous forme de comprimés ou de suppositoires; ceux-là sont employés de préférence dans la soirée de la deuxième journée post-opératoire alors que ceux-ci donnent les meilleurs résultats pendant la troisième journée. Aucun effet secondaire ne fut noté. La sédation post-opératoire ne semble exercer que très peu d'influence sur l'action du bisacodyl. Son mode d'administration simple et facile en fait un laxatif idéal pour les cas de chirurgie.

LES MEDECINS SONT-ILS CONTRE L'ASSURANCE-MALADIE SOCIALE?

"Les organes des caisses-maladie prétendent constamment dans leurs publications que les médecins contestent à l'assurance-maladie sociale sa raison d'être. D'après eux, "le plus gros obstacle à l'entente est que la direction centrale des organismes médicaux, tout au moins, considère les caisses-maladie comme un mal, et même pas comme un mal nécessaire".

Sur quoi les caisses-maladie se basent-elles pour lancer pareille assertion? Depuis des décennies, le corps médical se défend contre le flot montant de l'assurance-maladie sociale avec tiers payant. Nous nous sommes, depuis tout aussi longtemps, élevés contre l'extension croissante des assurances sociales, grâce à laquelle de larges couches de la population en sont venues à s'assurer les avantages de concessions que les médecins avaient faites à l'origine en faveur des économiquement faibles. C'est cette position de défense du corps médical que l'adversaire considère, ou du moins présente, comme une offensive dirigée contre l'assurance-maladie sociale en soi. Cette attitude prouve que la plupart des dirigeants de caisses qui jouent un rôle actif dans l'assurance-maladie ne peuvent se la représenter autrement que sous sa forme actuelle. Toute critique dénonçant certains anachronismes—comme l'expansion arbitraire de l'assurance-maladie et le tiers payant pour la totalité des membres qui prévaut dans la plupart des cantons—vise, à leurs yeux, l'assurance-maladie elle-même."—*Schweiz. Arzteztg.*, 40: 139, 1959.

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Case Reports

COXSACKIE PERICARDITIS

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SINCE Dalldorf and Sickles isolated the Coxsackie viruses in 1947, the pleomorphic nature of the disease processes produced by these organisms has become increasingly obvious. For some time it has been recognized that meningitis, meningoencephalitis, epidemic pleurodynia, herpangina and orchitis may occur, singly or in combination, in the course of such infections. More recently the involvement of the myocardium has been demonstrated,[1-3] and the complete and beautifully documented studies of the group from South Africa[4-7] are particularly convincing. Idiopathic benign pericarditis (I.B.P.) has for some time been suspected of being due to a virus infection, partly because no other cause was obvious and partly because the condition had not infrequently been noted in association with diseases long recognized as of virus etiology. Weinstein[8] described a case of acute benign pericarditis in which a significant rise of antibody titre to Coxsackie virus group B type 5 was demonstrated. Fletcher and Brennan[9] published a similar case in which antibodies to Coxsackie B4 were found. Movitt *et al.*[10] made further progress by recovering Coxsackie virus from the stools of two adult patients with pericarditis, and by demonstrating in each a rise in the appropriate antibody. McLean and his colleagues[11] have recently added to the evidence by publishing four cases of benign pericarditis in children (together with nine of epidemic pleurodynia), all of whom had Coxsackie B5 in the fæces and showed a rise in antibody titre.

The case for abandoning the term "idiopathic" for such cases is thus very strong, and we would perhaps be justified in using the descriptive phrase acute viral pericarditis for the majority of cases. We wish to add to the record a further adult case of proven Coxsackie infection in which an unusual variety of signs and symptoms was manifested, including those of pericarditis.

R.A., a white male medical laboratory assistant, aged 31, noticed symptoms first on October 12, 1958, when he complained of malaise, headache and slight sore throat. Like many persons within the medical milieu he decided to treat himself, but symptoms persisted and an increase in the severity of the headache prompted him to report sick on October 16. He was found to be febrile (101° F.) with a pulse rate of 100 and a normal respiratory rate. The only physical signs detected were a mild injection of the fauces and slight neck stiffness. A chest radiograph was negative. The hæmoglobin level was 13.5 g. %, white blood cell count 9000 with normal differential count,

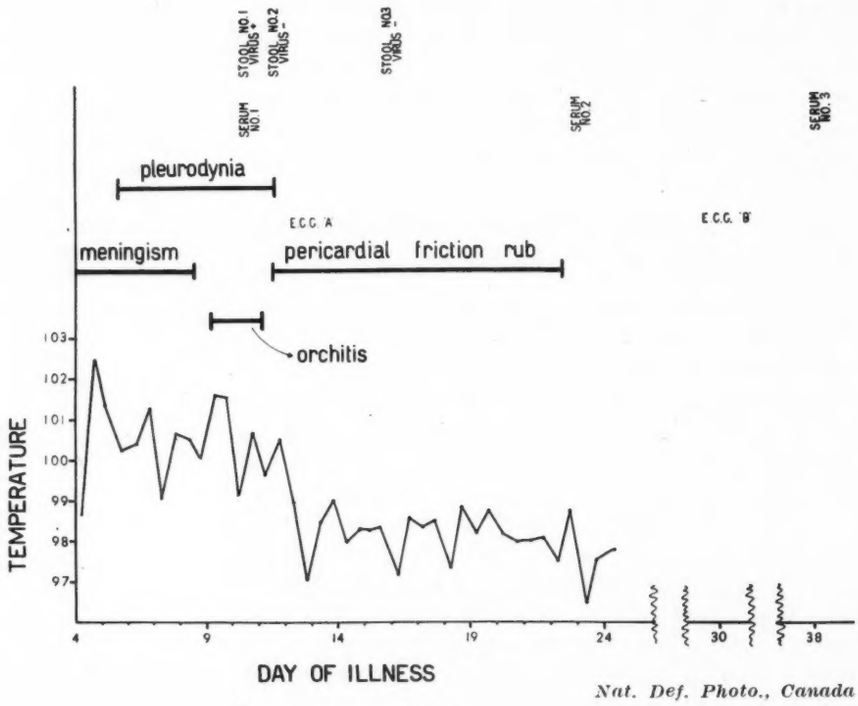

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Fig. 1.

erythrocyte sedimentation rate 23. The urine showed a specific gravity of 1017, no albumin or sugar and, microscopically, scattered pus cells, a few epithelial cells and an occasional unidentified cylindroid. He did not appear very sick but was admitted for observation. On October 17, he still complained of headache, vertigo on rising to the sitting position, stiffness of the neck and pain in the left side of the chest and left shoulder aggravated by breathing. The fauces remained injected, but at no time were any lesions resembling herpangina seen. Lumbar puncture was not performed because the patient was not very willing and because it was felt that the confirmatory evidence it would have offered did not justify insistence on the procedure, particularly as the neck stiffness and headache were subsiding and a diagnosis of bacterial meningitis was most unlikely. Aureomycin 250 mg. 8-hourly was administered but with no obvious effect. He remained febrile with a swinging temperature (Fig. 1) for several days. The white cell count remained in the vicinity of 10,000, and nothing pathogenic was cultured from the fauces. He continued to complain of pain in the left chest on breathing, though the radiograph

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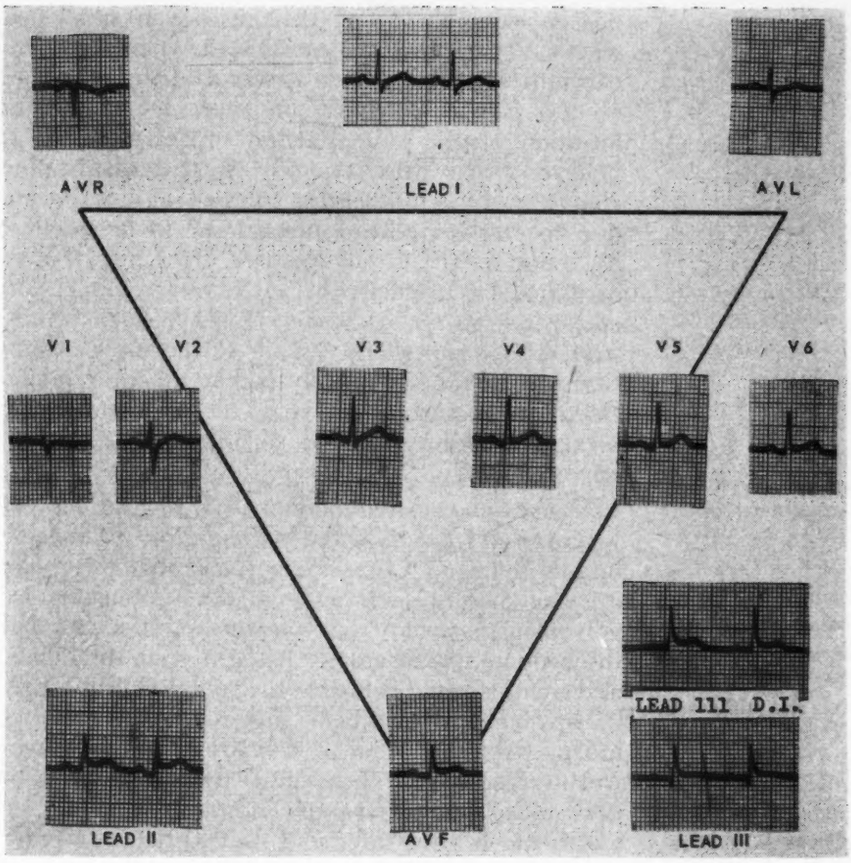

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Fig. 2.—Electrocardiogram A taken on October 24, 1958.

remained negative. On October 21, he developed pain in both testicles, and these were tender to palpation though not obviously swollen or inflamed. This lasted about 48 hours. By October 23, the febrile phase was subsiding but he remained rather weak and was noted to be dyspnœic on minor exertion. On this day, for the first time a very loud friction rub became audible over the whole of the precordium but maximal along the left sternal edge. The heart was not enlarged clinically though the radiograph showed a minor degree of enlargement. The heart sounds were loud and apparently normal, though auscultation was somewhat hampered by the loud friction rub. There was no venous congestion and no evidence of paradoxical behaviour of either venous or arterial pulse on inspiration.

On October 24, an electrocardiogram (Fig. 2) demonstrated S-T elevations in leads II, III, IIID.I., AVF, V5 and V6, which, though minimal, were consistent with pericarditis.

The patient was kept at strict bed rest and his remaining symptoms rapidly subsided. The friction rub remained audible till November 3, and during this time no increase in heart size or evidence of pericardial effusion was demonstrated. After this, he was allowed to take exercise gradually but he became tired and dyspnœic very easily and his pulse rate remained elevated even at rest. While these phenomena are known sequels of many severe virus infections, we felt it at least possible that the myocardium was involved and thought it wise for him to progress very cautiously towards full activity. On November 10, an electrocardiogram (Fig. 3) showed frank T wave inversions in leads II, III, IIID.I. and AVF and all precordial leads. Since then tracings have shown changes towards normality. On December 11, he was asymptomatic and clinically normal and was returned to duty.

Isolation of Virus

Stools were collected on the 6th, 7th and 12th days of illness. A 1:10 emulsion of each was prepared in balanced salt solution, penicillin and streptomycin were added, and 1-ml. quantities were used for infection of monkey kidney cell tissue cultures. After six days' incubation at 37° C. cytopathogenic effect was observed in the culture infected from the 6th-day specimen. Further tissue cultures were infected, a total of six serial passages being made. It was also found possible to pass the virus from monkey kidney cell cultures to human amnion tissue cultures.

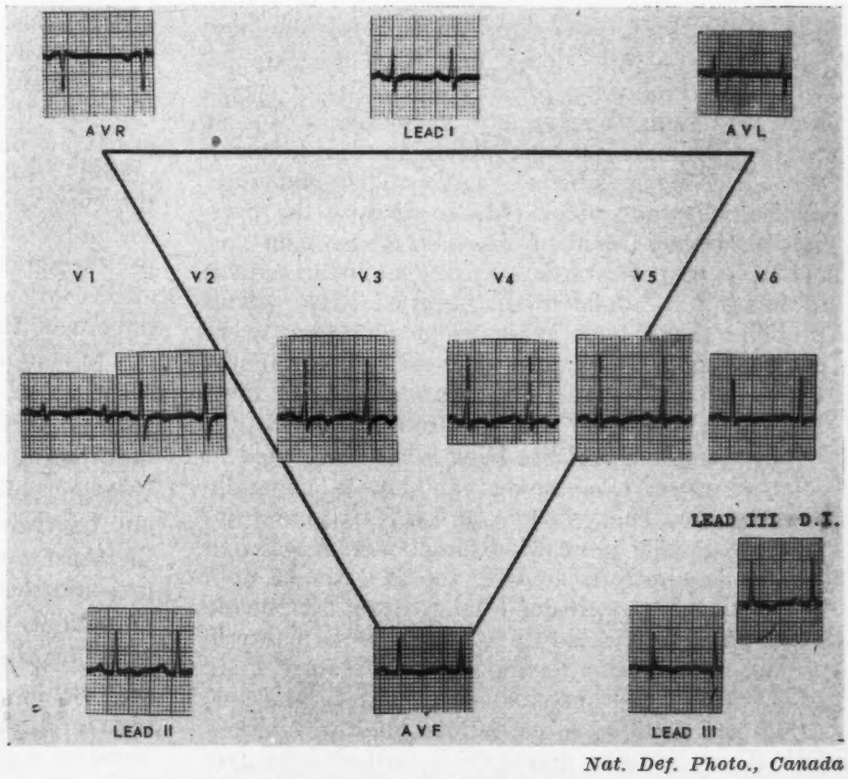

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Fig. 3.—Electrocardiogram B taken on November 10, 1958.

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Typing of Virus

The CPE producing agent grown from stool on tissue culture was subjected to neutralization tests against type-specific antisera. The range employed included Coxsackie A9, B1, B2, B3, B4 and B5 antisera. Specific neutralization of the unkown virus by B5 antiserum was demonstrated. Duplicate typing tests conducted at the School of Hygiene, University of Toronto, confirmed the presence of Coxsackie B5 virus.

Three litters of randomized 24-hour-old mice were inoculated intracerebrally (0.02 ml.) and three litters intraperitoneally (0.05 ml.), using each of the three 10% stool suspensions. These animals were observed for a period of 14 days, during which time they remained healthy. Two litters of mice of a similar age were inoculated both intracerebrally and intraperitoneally with monkey kidney tissue culture fluid. From the litter inoculated intraperitoneally, two mice showed paralysis of the forelegs after six days. Histological sections of skeletal muscle showed no lesions. Changes characteristic of Coxsackie B virus infection were observed in the interscapular hibernating gland fat pads. These included peripheral congestion, necrosis, infiltration with inflammatory cells and intercellular granularity. Sections of brain showed no marked changes.

Virus Neutralization Studies

Serum No. 1 from the patient, collected on the 11th day of illness, neutralized Coxsackie B5 virus in a dilution of 1:128. Serum No. 2, collected on the 23rd day of illness, showed a rise in titre to 1:1024. Serum No. 3 (38th day) neutralized in a dilution of 1:512.

DISCUSSION

This case thus fulfils the criteria laid down by Kilbourne[12] for a proven and specific virus etiology. There can be little doubt that the Coxsackie B5 virus was responsible for this miscellany of symptoms and signs. The variety of symptoms was of course invaluable in diagnosis, and in fact the case had been labelled a Coxsackie infection clinically by one of us (M.J.L.) before the pericarditis became evident. Had the chest pain and evidence of pericarditis occurred alone in a man of this age, a confident diagnosis of I.B.P. would probably have been made. The symptoms were never such as to suggest myocardial infarction—the condition regarded by Reid *et al.*[13] as most likely to be confused with this form of pericarditis.

The term "benign" has been widely accepted in relation to this condition, and it is generally assumed that the outcome of I.B.P. is almost invariably good if pericardial tamponade is watched for and promptly treated. In the 23 cases of Reid *et al.*[13] there was only one fatality—from tamponade—and apparently there was a return to normality in all the others. In a review of the literature Price *et al.*[14] could find only four cases with a fatal outcome, and of these three patients died in tamponade. These authors described a further fatal case in which a large pericardial effusion was found post mortem. Not all of these cases were published with full pathological reports, but when the myocardium was reported on it was said to be normal except for a polymorphonuclear leukocyte infiltration of the subepicardial myocardium. It is believed that the typical electrocardiographic changes, which may persist for several months, are due to this superficial myocardial involvement.[15] At times the ECG changes are gross and it may be difficult to reconcile them with only a minor subepicardial lesion. However, Kisch[16] has demonstrated that superficial lesions of the myocardium have a disproportionately great effect on the electrocardiogram, and that these lesions may be structurally so minor as to be difficult to detect microscopically.

The article by Simenhoff and Uys[5] and that of Javett *et al.*[3] describe the pathological findings in infants dying of Coxsackie myocarditis, and make it clear that in such patients the myocardial involvement is severe and widespread. It seems that the neonate is particularly liable to such infections, and there is some evidence that older children may be involved.[17] It has been suggested that neonates are particularly prone to develop Coxsackie myocarditis because of their high circulating levels of corticoids. Adult mice are normally resistant to Coxsackie B virus infections, but Kilbourne *et al.*[18] were able to produce extensive myocardial damage by giving cortisone to the inoculated animals. These authors speculated on the possible dangers of converting benign viral disease in adult patients to a much more serious infection by the untimely use of corticoids.

At present there seems to be no positive evidence for the occurrence of widespread or serious Coxsackie myocarditis in adult patients, and the available pathological data, though scanty, certainly do not indicate any lasting myocardial damage. The case of Fletcher and Brennan,[9] however, showed numerous premature contractions persisting over a period of two months, and they wondered whether this was due to myocardial involvement. It is certainly hard to understand how an exclusively pericardial or epicardial process could produce this effect. Myocarditis not infrequently complicates poliomyelitis, and we think that it would be dangerous to assume that myocarditis never occurs in the acute phase of adult Coxsackie infections. We have been impressed by the dyspnœa and persistently high pulse rates shown by patients in the convalescent phase of I.B.P. when tamponade could not be demonstrated and the hæmodynamics of the heart were apparently unimpaired. In any case, it would seem prudent to withhold corticoids from all patients suspected of suffering from a Coxsackie infection and certainly from all acute cases of pericarditis unless a diagnosis of rheumatic infection is unequivocal. It would also seem wise to insist on a prolonged convalescence from I.B.P. so far as this is feasible.

We wish to express our indebtedness to Professor C. E. van Rooyen for his interest and for the enthusiasm with which he placed his experience and specialized facilities at our disposal.

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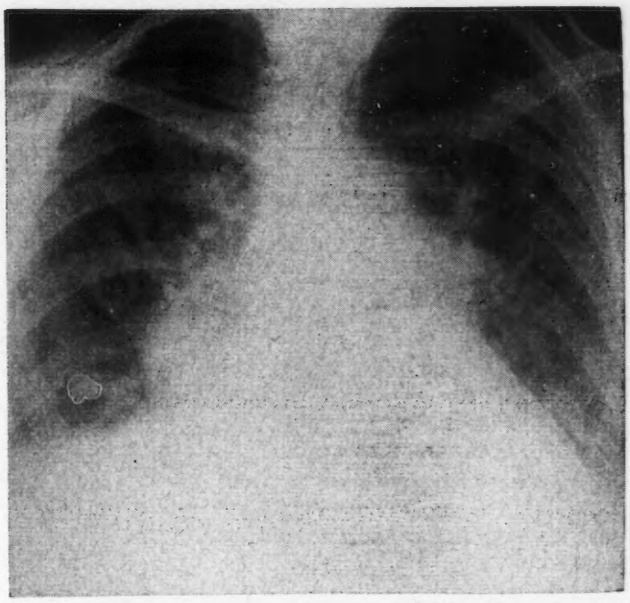

Fig. 1.—Chest radiograph (October 18, 1958), 12 hours after admission, indicates generalized cardiac enlargement and pulmonary congestion. There is a density in the right lower lung field consistent with a pneumonic consolidation.

CONGESTIVE HEART FAILURE CAUSED BY SENSITIVITY TO DIPHENYLHYDANTOIN (DILANTIN SODIUM)

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FOR THE PAST quarter-century, it has been known that a non-antigenic chemical may unite with blood protein to form a specifically reactive antibody.[1] Drugs in common usage, such as sulfonamides, iodides, Dilantin sodium (diphenylhydantoin), phenobarbital, arsenicals, and thiourea, may incite hypersensitivity reactions indistinguishable from serum sickness, periarteritis nodosa, and hypersensitivity angiitis. Because they are so commonly used, consideration of their role in the etiology of unusual vascular and systemic syndromes[2] is important. The lesions may vary from subacute to acute, with involvement of the intimate vasculature of the skin and any or all of the viscera. Myocarditis, pneumonitis, nephritis, or diffuse dermatitis may predominate. The medical condition is frequently alarming and may be fatal.

The following report describes an acute hypersensitivity reaction related to the use of Dilantin sodium. The salient clinical feature was rapidly developing congestive heart failure.

A.T., a 49-year-old white woman, hotel manager, was first admitted to the service of Dr. J. Mayer at the New Mount Sinai Hospital, Toronto, on September 12, 1958, and discharged after investigation on September 19, 1958. During the preceding four months, she had suffered three attacks of grand mal convulsions without aura. In each case, the attacks had occurred about one week before menstruation. Her previous health had been normal. She was a robust-appearing, moderately overweight woman. Her height was 63 in., weight 167 lb., blood pressure 120/80 mm. Hg, pulse rate 80. There were no abnormal physical findings. The heart was of normal size with regular rhythm and no murmurs. The urine was normal, grossly and microscopically. The hæmoglobin value was 15.5 g., W.B.C. 7400, blood smear normal. The blood Wassermann reaction was negative. Lumbar puncture revealed a spinal fluid pressure of 150 mm. H_2O, one white and one red cell, protein 17 mg. %, colloidal gold 012210000; fasting blood sugar 108 mg. %, N.P.N. 33 mg. %. An air encephalogram was normal. A diagnosis of idiopathic grand mal epilepsy was made, after which the patient was sent home on a maintenance dose of 0.1 g. diphenylhydantoin (Dilantin sodium) 3 times a day.

She remained symptom-free until October 15, 1958. On this date, fever and rash appeared. Despite this she continued on medication. Three days later her physician examined her at home and noted a well-marked maculopapular rash involving the face, trunk and extremities. The oral temperature was 103° F. There were no other findings. The diphenylhydantoin was discontinued. On the next day, I was asked to see her by her physician because of a serious deterioration in her clinical state. On examination she was orthopnœic and cyanosed. The oral temperature was 102° F., respiration rate 35, pulse rate 130, blood pressure 110/70 mm. Hg. Auricular fibrillation was present. There were coarse and fine rales throughout both lung fields, particularly in the right base. The neck veins were distended. The liver was two fingers'-breadths below the costal margin, enlarged and tender. The rash was still brilliant. The patient was admitted to hospital immediately. On arrival, oxygen therapy was instituted. Twenty-five units of ACTH and 1 mg. of digoxin were administered intramuscularly; 8 mg. of triamcinolone was given orally, with repeated doses of 4 mg. 4-hourly. The next morning she was more comfortable. Auricular fibrillation persisted with an apical rate of 110. The temperature had fallen to 100°

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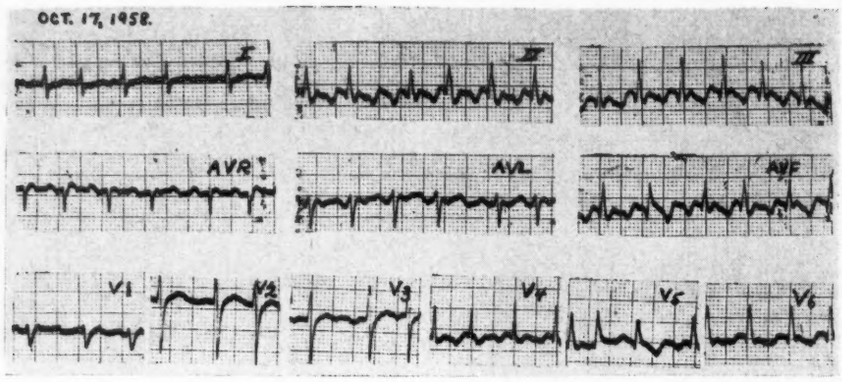

Fig. 2.—Coarse auricular fibrillation. The T waves in leads 1 and V6 are of low amplitude.

F. There were persistent medium rales in the right base but the neck veins were not full. Oral digoxin was continued. Laboratory findings at this time were as follows: Hb. 13.0 g. %; W.B.C. 13.7; R.B.C. 4.42; differential neutrophils 65%, lymphocytes 29%, monocytes 6%; sedimentation rate 33 mm. (Westergren). Urine negative for sugar and albumin, S.G. 1005, microscopically negative. The blood sugar was 130 mg. %, N.P.N. 34 mg. %. A chest radiograph (Fig. 1) showed generalized cardiac enlargement with increased prominence of the hilar and peripheral vessels. There

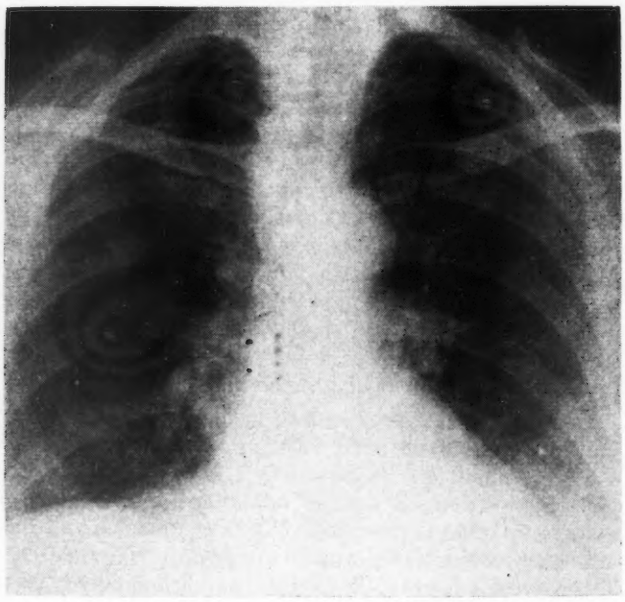

Fig. 3.—Second chest radiograph (October 28, 1958), 10 days later, shows clear lung fields and marked decrease in cardiac size.

was a small amount of pleural effusion at the left base and a triangular density at the right base consistent with pneumonitis. The electrocardiogram (Fig. 2) showed auricular flutter fibrillation with rapid rate. T1 and TV6 were of low amplitude. On the third day in hospital the temperature was 98.8° F. and the pulse rate 90 but irregular. Quinidine sulfate therapy was started with conversion to normal sinus rhythm on the fourth day in hospital. The pulmonary signs rapidly cleared, and by the sixth day in hospital, digoxin was discontinued and triamcinolone reduced to a maintenance dose of 8 mg. On the eleventh day, the patient was quite well and receiving no medication. The white cell count was 8700, neutrophils 18%, lymphocytes 57%, monocytes 23%, eosinophils 2%. The chest radiograph (Fig. 3) now revealed no significant cardiac enlargement, and clear lung fields. The electrocardiogram (Fig. 4) was normal. She was discharged on October 27. She remained well and was last examined at the office on December 8, 1958. At this time the electrocardiogram was normal, and fluoroscopy did not indicate any cardiac enlargement. Throughout her entire illness there were no cardiac murmurs.

DISCUSSION

After continued use of diphenylhydantoin for one month, this woman developed acute hypersensitivity involving the skin, heart, and lungs. It is reasonable to assume that the drug alone produced this reaction in the absence of other etiological agents, the negative subsequent follow-up, and the dramatic response to steroid therapy. The latter apparently eliminated a dangerous antigenic reaction present when the patient was first seen.

Diphenylhydantoin has known effects upon the electrocardiogram. These are minor in nature and are rarely associated with clinical findings. Finkelman and Arieff[3] noted P-R prolongation, decreased amplitude of T waves, and QRS changes in over 50% of cases. Postmortem findings in patients dying of hypersensitivity to the drug have also been reported. VanWyk and Hoffman[4] noted myocardial œdema in one case in which severe necrotizing vascular lesions were seen in other viscera. In a study of eight deaths due to diphenylhydantoin hypersensitivity, Blair[5] noted two in which the myocardium showed infiltration of inflammatory cells and degeneration of the myofibrils. The clinical and pathological findings are similar to those noted in many cases due to sulfonamide hypersensitivity.[2, 6-8] The rarity of clinical reports similar to the one presented would indicate that congestive heart

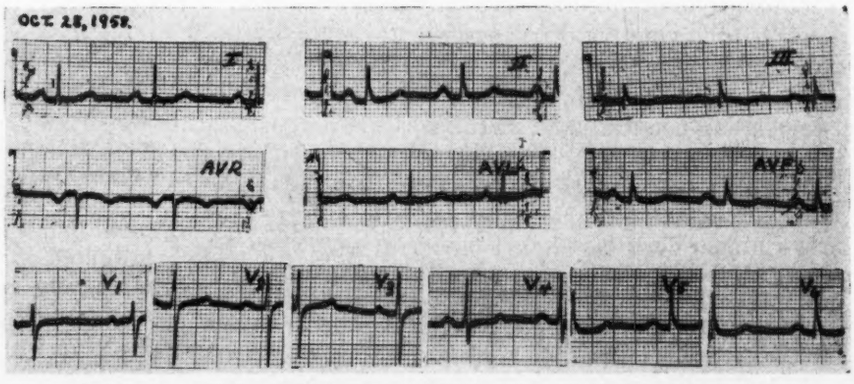

Fig. 4.—Normal sinus rhythm. The record is within normal limits.

failure resulting from hypersensitivity to diphenylhydantoin is an unusual syndrome. It is suggested that steroid therapy may prove of considerable benefit in clinical hypersensitivity states in which myocardial involvement is suspected.

SUMMARY

A case is presented in which acute myocardial failure was associated with hypersensitivity to diphenylhydantoin (Dilantin sodium). An apparently grave clinical situation was promptly reversed by steroid therapy. There were no cardiac residual signs.

The author wishes to thank Dr. H. Winesanker for his assistance and referral of this case.

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GIANT-CELL TUMOUR OF BONE INVOLVING THE SUPERIOR RAMUS OF THE PUBIC BONE*

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THE OCCURRENCE of a giant-cell tumour of bone involving the pubic bone is extremely rare. A review of the literature over the past 20 years revealed no report of a giant-cell tumour in this location, and publication of the following case therefore appears justified.

A 29-year-old man fell at work and sustained a minor injury to his right gluteal region. The patient complained of pain in his right hip while walking and of tenderness in his pubic region and right groin. An x-ray examination at that time revealed a lytic lesion involving his right innominate bone.

Physical examination.—There was a suggestion of a mass on deep palpation above the right inguinal ligament, and some tenderness in the right groin. No increase in local skin temperature was noted.

Temperature, pulse, respiration and blood pressure were normal. A complete blood count disclosed no abnormalities.

X-ray examination including a urogram showed a monostotic lesion arising in the lateral portion of the superior ramus of the pubic bone extending into the

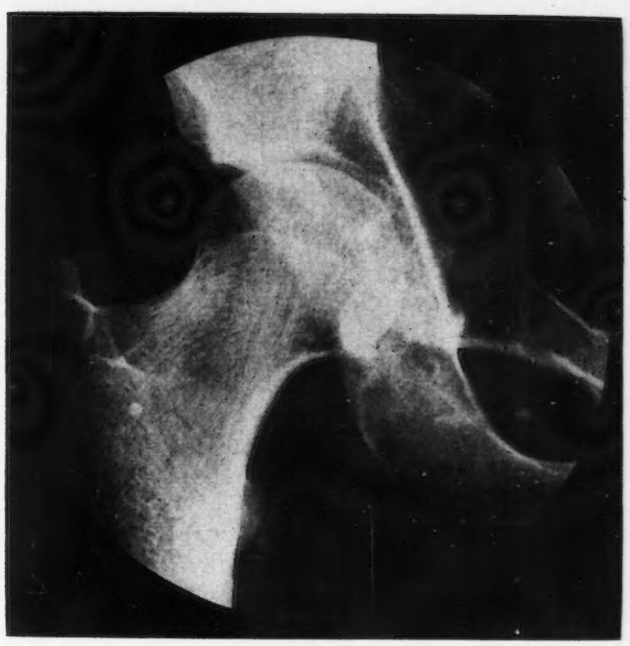

Fig. 1

pubic portion of the acetabulum (Fig. 1). Medullary in origin, it had grown beyond the normal confines of the pubic ramus, producing a soft tissue mass. The internal pattern of the tumour was uniform in appearance except for the presence of a few widely scattered fine lines of increased density projected over the soft tissue mass, representing fractional trabeculæ.

The medial boundary of the tumour was a smooth curve and showed a gradual transition from soft tissue density of the tumour to that of the adjacent bone. No expansion of the cortex was noted. The bony shell was destroyed along the superior margin and atrophied along the inferior margin of the bone defect.

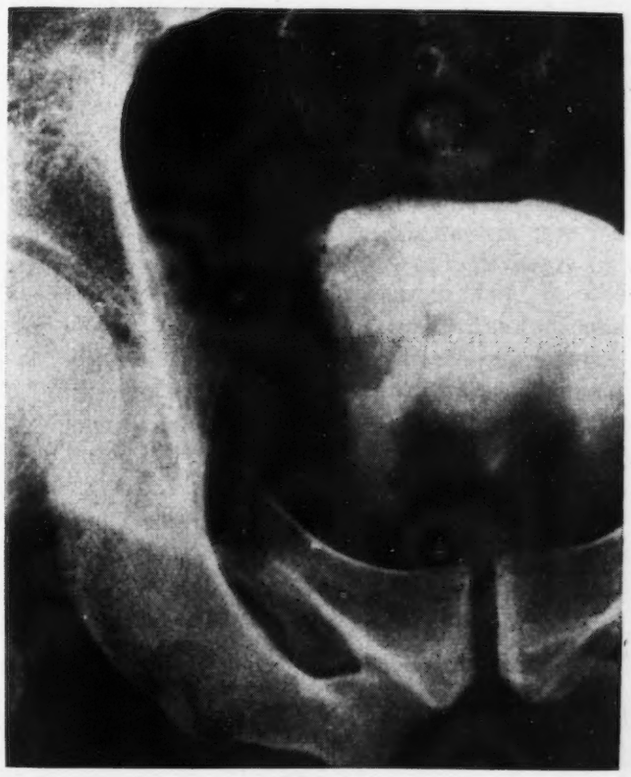

Fig. 2

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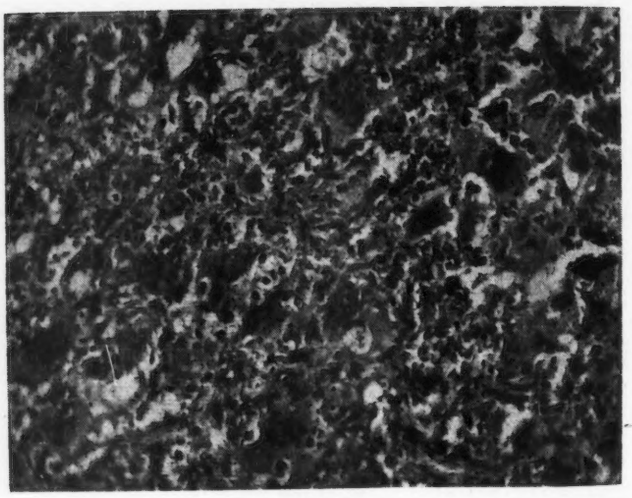

Fig. 3

An intravenous urogram and cystogram showed evidence of an extrinsic pressure defect on the lateral aspect of the bladder. Radiographs of the spine and chest were normal (Fig. 2).

A biopsy was performed on the 10th day in hospital and the histological diagnosis of benign giant-cell tumour of bone was made (L. S. Mautner). In view of the unusual location and the confusion as regards correct diagnosis of a lesion showing giant cells, a photomicrograph of a representative part of the tumour is shown (Fig. 3). The tumour has been registered in the Bone Sarcoma Registry of the A.F.P.I. as a giant-cell tumour.

On the 40th day in hospital a laparotomy was performed and revealed a huge demarcated mass measuring 14 x 7.5 cm. and consisting of reddish-brown friable tumour tissue. Most of the pubic ramus had disintegrated, leaving only a shell anteriorly and inferiorly. The entire superior ramus was removed together with all other involved portions. The bone was thoroughly curetted out, well down into the spine of the ischium. It was felt the tumour had been completely excised by this process.

DISCUSSION

The differential diagnosis should include aneurysmal cyst of bone which is rare in this location and age group and is more trabeculated, while a thin shell of bone representing new bone formation is seen in most cases.

A chondroblastoma usually has a sharply demarcated sclerotic margin.

Osteolytic osteogenic sarcoma, solitary myeloma, reticulum cell sarcoma and eosinophilic granuloma would further have to be considered.

Since Jaffe and Lichtenstein identified many of the lesions formerly classed as giant-cell tumour as distinct clinical and pathological entities, the accurate identification of lesions of this category is of considerable practical importance.

Many authors, including Lichtenstein, do not feel that the x-ray appearance of the giant-cell tumour is absolutely diagnostic, and although this has been contradicted by Brailsford, there appears to be some agreement that the x-ray appearance in flat bones is simply an area of rarefaction lacking in distinguishing characteristics.

SUMMARY

The case presented is one of giant-cell tumour of bone in an unusual location, meeting current histopathological criteria for this definite entity.

Age and clinical picture are in keeping with the diagnosis of giant-cell tumour.

The x-ray appearance was uncharacteristic, a usual finding for giant-cell tumours in flat bones.

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MULTIPLE DIVERTICULITIS OF THE CÆCUM

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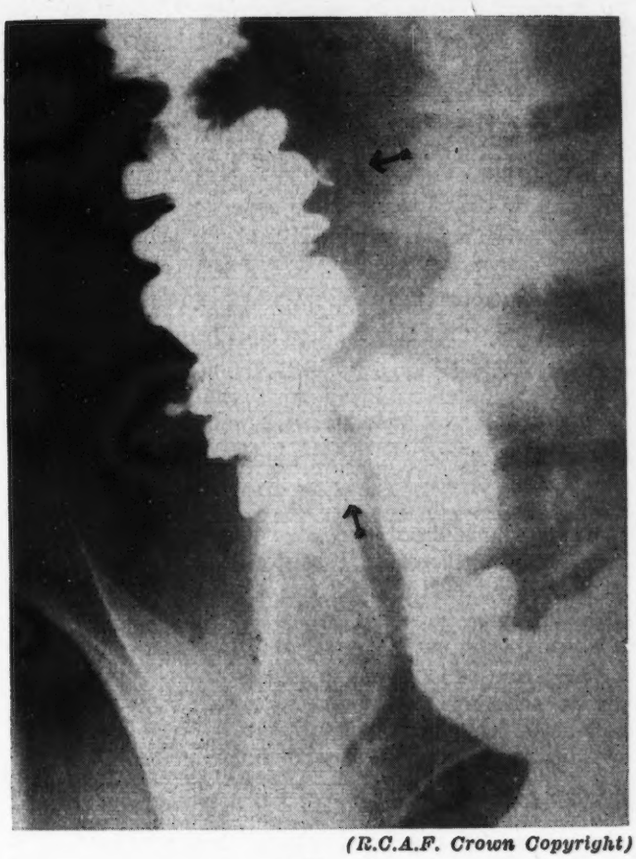
RIGHT LOWER QUADRANT pain is a frequent and challenging diagnostic problem. Diverticulitis of the cæcum is such a rare cause of this symptom that the following case may be of interest.

The patient, a 186-lb., 24-year-old aero-technician, was admitted to the R.C.A.F. 3 (F) Wing Hospital for investigation of recurrent low right abdominal pain.

Until two years previously he had been perfectly well. One day, about that time, he developed an odd feeling of "something moving" in his right lower abdomen. This subsided in about eight hours, but on the following day he developed sharp right lower abdominal pains, radiating to the left across his lower abdomen. These pains came in waves lasting minutes, and about every hour, continuing for two days. They were not accompanied by nausea, vomiting, or abnormalities of urine or stools.

About six months later a similar attack developed, and some six months after that, yet another. From that time he averaged about one attack a month, with a progressive increase in their frequency and severity. He noted that if he had a few drinks during an evening, he would almost invariably get an attack late next morning, and there was a suggestion of relief from food. The majority of his attacks, however, started about 9 p.m. with no obvious precipitating cause. The patient was finally admitted to hospital



(R.C.A.F. Crown Copyright)

Fig. 1

because of an attack of two days' duration, which was producing waves of pain almost severe enough to "double him up". His general health had remained good throughout this series of attacks. Past and family history were not remarkable.

His highest temperature was 99.2° F. during the first three days in hospital; it then rose sharply to 103° F., with an attack of the current epidemic of influenza. The temperature fell to normal two days later and he remained afebrile. His pulse was normal except during his influenza attack. The only significant finding on examination was a localized area of deep tenderness in the right lower quadrant in the region of McBurney's point. Routine laboratory studies revealed: Hb. level 15.7 g. %, W.B.C. 11,400, E.S.R. 8 mm. in one hour. Two out of three stool specimens were positive for occult blood, but all were negative for parasites.

The clinical impression at this time favoured a chronic appendicitis. Investigation was undertaken to exclude possible regional ileitis or duodenal ulcer, or demonstrate a Meckel's diverticulum.

The barium meal examination showed some hypertonicity and spasm of the stomach and duodenum, but no ulcer.

With the barium enema (Fig. 1), no deformity was noted in the transverse, descending or sigmoid colon, but a marked narrowing, deformity, and absence of the normal mucosal pattern were visible in the pole of the cæcum and, to a lesser extent, in the proximal part of the ascending colon. A number of diverticula were also to be seen in the cæcum and proximal part of the colon, the latter feature being more clearly demonstrated by the follow-through of the barium meal when examined at two hours, at which time the diverticula were seen to be filled more completely. Some delay in the emptying of the small bowel was also noted at this last examination. Altogether, about six diverticula could be seen in the cæcum and ascending colon. Had there been no visible diverticula, the appearance of the cæcum simulated what might be expected in a tuberculous or neoplastic condition of the cæcum.

Laparotomy was performed on November 26, 1957, 24 hours after a single 4-g. oral dose of neomycin. The adiposity and local adhesions encountered at operation obscured the lesion and influenced the decision to perform a right hemicolectomy in preference to a more limited resection. An end-to-side anastomosis was carried out between the terminal ileum and the proximal transverse colon. His subsequent hospital course was uneventful and he was discharged on the 11th postoperative day. At follow-up six months later he was found to have maintained his weight, was free of abdominal pain, and was having two well-formed stools daily.

The pathology department reported that the appendices epiploicæ contained much fat which showed induration in the area near the ileo-cæcal valve. The serosa was smooth and glistening. The mucosa of the cæcum, near the ileo-cæcal valve, showed two openings measuring 0.2 cm. in diameter which allowed the probe to be inserted for about 0.1 cm. The surrounding tissue was slightly indurated. The appendix was normal.

Microscopically the cæcum was lined by normal epithelium showing many round cells between the glands. The submucosa was œdematous. Some granulocytes were seen in the serosa and occasionally between the musele strands. Another section showed a deep outpouching of the epithelium into the surrounding fatty tissue. This outpouching was surrounded by a thin layer of stretched fibrous tissue and some smooth muscle. Chronic and acute inflammatory cells were seen in the surrounding tissue.

DISCUSSION

In 1952, Lauridsen and Ross[1] published a comprehensive review of diverticulitis of the cæcum. Of the 153 cases they collected, only six had more than one diverticulum. Only four cases were diagnosed correctly preoperatively, and two of these persons had had a previous appendectomy. The commonest preoperative diagnosis was acute appendicitis (85%). In approximately 30% of cases, the correct diagnosis could not be established even at operation; malignancy was the commonest misdiagnosis because of the presence of induration and adhesions.

Clinically, it is impossible to distinguish this condition from appendicitis. However, in the series quoted, nausea (27%) and vomiting (16%) were uncommon, whereas they are an almost constant feature of appendicitis. Radiological examination is the only reliable means of making the diagnosis. It is interesting to note that the condition was more completely demonstrated by the barium meal follow-through technique than by the retrograde barium enema method.

The diverticulum of the right colon differs from that of the left in the following respects:

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1. It is congenital rather than acquired, as demonstrated by embryological developmental studies.[2]

2. It is a true diverticulum with demonstrable muscle fibres in its walls.

3. It is usually solitary.

4. It is found at an earlier age. Lauridsen and Ross reported the median age in their group to be 39 years, and the youngest 10 years.

5. The same authors found the incidence about equal in the two sexes, whereas left-sided diverticula have approximately a two-to-one male preponderance.

The two conditions differ in management also, as that of diverticulitis of the cæcum and the ascending colon is always surgical.[3] Conservative management, by diet and bowel regulation, can do little to influence the formation of semi-fluid stools when diverticula are at this level.

In the presence of the usual acute solitary lesion which mimics acute appendicitis, simple diverticulectomy is the procedure of choice. In contrast, when confronted with an unknown cæcal lesion it is well to remember that malignancy, tuberculosis, actinomycosis, and diverticulitis may be responsible, in that order of frequency. Radical surgery under suboptimal conditions has a particularly unrewarding mortality rate. All available evidence should be mustered from palpation (some operations have successfully identified the ostium or its obstructing fæcalith), the condition of the liver, regional lymph nodes and peritoneum, and frozen section if available.

In the case presented, because of the multiplicity of the lesions, the choice was between local resection or hemicolectomy. The latter was selected because (1) technically the procedure is simpler; (2) the identification of the upper limit of the involved bowel, in the presence of adhesions and adiposity, was impossible; and (3) ileo-transverse colostomy is a safer anastomosis than ileo-ascending colostomy.

SUMMARY

A case of multiple diverticula of the cæcum and ascending colon, diagnosed preoperatively, is presented.

Barium enema, or follow-through from a barium meal, is the only preoperative diagnostic means.

Pathological examination confirmed the characteristics of true diverticula.

Treatment is always surgical, and in this case was by right hemicolectomy.

The authors wish to express their thanks to Major M. H. Sulak of the Pathology Department, USAREUR Medical Laboratory Center, Landstuhl, West Germany, for the pathological study of the specimen.

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Special Article

AN INTEGRATED MEDICAL SERVICE FOR THE AGED
A PATTERN FOR AN ACTIVE MEDICAL PROGRAM IN A HOSPITAL FOR CHRONICALLY ILL AND A HOME FOR AGED AS EVOLVED THROUGH INTEGRATION WITH A GENERAL HOSPITAL

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THE PURPOSE of this communication is to present the overall medical program that has been developed at the Baycrest Hospital for Chronically Ill and the Jewish Home for the Aged through integration with the New Mount Sinai Hospital, Toronto.

Some of the major problems that have confronted homes for the aged and hospitals for chronic diseases are the matters of adequate interested staff and a working dynamic program. To achieve such an aim at Baycrest Hospital and the Jewish Home for the Aged, it was felt that the best way was to integrate the medical services of this institution with those of the New Mount Sinai Hospital. A plan was elaborated whereby the overall medical staff as well as the junior interns from the New Mount Sinai Hospital would serve on a rotating basis at Baycrest Hospital and Jewish Home for the Aged. An educational program involving the staff was started in order to stimulate interest in the field of geriatric medicine and modern concepts in the care of the aged and chronically ill. In order to provide a further stimulus for all concerned, a program of clinical research was initiated.

JEWISH HOME FOR THE AGED AND BAYCREST HOSPITAL

This institution, situated on spacious landscaped grounds, consists of a modern three-storey building. It has facilities for living quarters (two in a room) for some 150 aged but well people on the first two floors. The third floor contains an 87-bed unit and is known as Baycrest Hospital. The hospital section is, for practical purposes, a self-sufficient unit and has provisions for a comprehensive active program for chronic diseases. Patients requiring major surgery are transferred to the New Mount Sinai Hospital.

The Home.—The Home has a clean, airy, bright and cheerful atmosphere about it, with usually two beds to a room. Solaria are situated at each end of a wing to provide space for various forms of recreational activities. A "beauty salon" and barber shop are provided for the residents. All well members have their meals in an attractive large dining room adjacent to the kitchen unit. Near the dining room are a tuck shop and an auditorium; the latter is used for meetings and entertainment. On

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the same floor there are situated a synagogue, study room and library for the spiritual and cultural needs of these people.

Medical care in the home.—This is provided by an adequate nursing and orderly staff and four part-time physicians, to each of whom are allocated some 50 residents as patients. These attending physicians are appointed on a yearly basis and thus provide continuity of service. The interns who serve in the hospital are responsible for the comprehensive initial history and physical examination of all persons admitted, including those to the Home, and for any urgent medical need. All residents in the Home and, of course, in the hospital have their history and physical examination and laboratory findings recorded in a specially designed chart. Should the individual in the Home require hospital care, he is transferred to Baycrest Hospital (on the third floor).

Special care section.—This division is situated on the ground floor of the institution and houses some 42 semi-senile and moderately senile patients. They are under the capable guidance of one of the four part-time physicians, who is assisted by an understanding and enthusiastic staff.

Baycrest Hospital.—This is an 87-bed unit hospital for the chronically ill and the incapacitated. They may be admitted on transfer from the Home, but the majority of patients are admitted from outside the institution. The wards are usually of the two-bed and four-bed variety, and all beds are of the high-low type easily raised or lowered by pressing a switch. The usual hospital setup exists here, with facilities for clinical laboratory and x-ray examinations, physiotherapy and occupational therapy. The nursing and orderly staff are under the management of the director of nurses. Over the years the quality of care has improved immeasurably.

Medical personnel.—(1) The physician-in-chief, who acts as liaison officer between this institution and the New Mount Sinai Hospital, co-ordinates all the medical services needed in the institution. He is chairman of the Medical Advisory Committee which recommends medical policies and programs, and represents the Medical Advisory Committee of the Baycrest Hospital and the Jewish Home for the Aged in the Medical Advisory Council at the New Mount Sinai Hospital.

(2) The associate physician-in-chief, who is an internist with wide experience in geriatric medicine, is director of geriatric studies. He directs the clinical work at Baycrest Hospital and in the Home, supervises and teaches the interns, and conducts an educational program with special emphasis on geriatrics. This program includes weekly rounds with the medical personnel, daily rounds with the interns, series of lectures to nurses and orderlies, lectures to patients and residents in the Home, and lectures to lay groups.

The care of the patients on the hospital wards has been assigned to the general practitioners' group of the New Mount Sinai Hospital. They are chosen in groups of about ten on a rotation basis for four months or longer. While on service at Baycrest, the physicians are excused from their duties in the out-patient department of the New Mount Sinai Hospital. They are given a relatively free hand in the management of the patient. In their capacity as clinicians, these doctors, by making an effort and taking advantage of their opportunities, cannot help but feel a certain stimulus that is lacking in their office practices. In the long run it tends to improve their knowledge, increase their experience in the management of long-term care patients, and ultimately lead to better service to their private patients.

The integration of the medical services with the New Mount Sinai Hospital provides a consulting staff in various fields of medicine. These men are also assigned duties on a rotating basis for periods varying from one to four months. During this time they are relieved of active service at the New Mount Sinai Hospital. Their duties include consultation service, when called upon by the attending physicians, and the holding of special clinics on a weekly or bi-weekly basis. Patients throughout the institution are referred to these clinics for special examinations and advice. These clinics, which provide an opportunty for the intern to receive personal tuition by the various specialists, are the nucleus of our proposed geriatric out-patient department.

A meeting of the attending doctors and consultants is held each week on a Friday morning, lasting one hour. As a rule, one case is presented by the intern and discussed in detail, with emphasis on interpretation of signs and symptoms, differential diagnosis and treatment of the case, in particular as they concern aged patients. Once a month, deaths of the previous month are reviewed and cases of special interest are discussed in detail.

As an aid to management of patients, the nursing superintendent and members of the staff in physical medicine, occupational therapy and social and recreational services are all invited to participate in these meetings in outlining the care of the particular patient.

To aid in the diagnosis and management of patients, there are various ancillary services, each under the direction of the respective chief of that service at the New Mount Sinai Hospital. A well-equipped x-ray department is available, employing a part-time technician, and is usually visited once a week by one of the radiologists. All permanent members of the staff, all residents and all patients have an annual radiograph of the chest.

There is a neat, compact clinical laboratory with facilities for doing a substantial amount of work. A full-time, qualified technician does most of the usual tests, excluding bacteriology.

Part-time psychiatrist.—In addition to the psychiatric staff of the New Mount Sinai Hospital, who serve on a rotating basis as consultants, there now is a part-time psychiatrist whose main functions are to advise the social service personnel and work with them, give regular lectures on mental hygiene, and indoctrinate the staff in the psychological aspects of the care of the aged, both the well and the sick. Continuity of care where indicated is also provided.

Physiotherapy.—Since rehabilitation is a major part of the program, this department continues to be a very active one. At present there are two full-

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time therapists under the direction of the chief of physical medicine of the New Mount Sinai Hospital.

Dental department.—A dental unit has been set up in Baycrest Hospital under the supervision of a member of the dental department of the New Mount Sinai Hospital. Here, too, members of the dental department are allocated on a rotating basis to Baycrest Hospital. Two clinic days a week are held to provide adequate initial survey and follow-up care. Plans for clinical research in this relatively fruitful field in the aged are in the offing.

Pharmacy.—A part-time pharmacist is at present in charge of preparing and dispensing drugs. The expansion of this institution, now in the process of planning, will require a full-time pharmacist to give adequate service.

An active interested social service group contributes greatly in carrying out the program.

CLINICAL RESEARCH

Over the past few years we have initiated a variety of clinical research projects, in which members of the staff as well as interns have participated. These projects have included:

1. Routine intraocular pressure examination, which has resulted in the finding of pressures raised above normal in some 44 patients.

2. Close scrutiny of signs and symptoms of peripheral vascular disease which has enabled us to detect 47 patients with moderate to severe degrees of this entity.

3. The use of an oral dye test in the detection of free acid in the stomach. This test was performed on some 125 patients. The results would indicate that it is reasonably accurate qualitatively and should prove quite useful because of its simplicity.

4. Routine sigmoidoscopic examination of all individuals in this institution, which has enabled us in 366 examinations to discover some 20 polyps, a few of which were malignant.

5. Use and evaluation of new drugs: With new drugs continually coming on the market, we have been able to run clinical trials with discretion on certain drugs. This applies particularly to patients with cardiovascular disease.

6. Investigation of gastro-intestinal complaints: By investigating these more fully, we were able to diagnose no fewer than 33 cases of hiatus hernia. The medical staff have become definitely more aware of this lesion in the aged. In three of these patients, a phrenicotomy was performed under local anæsthesia, because of intractability; two had marked anæmia and one persistent heartburn and vomiting. One patient has had an excellent result to date.

7. Diabetic control program: Because of the large number of diabetics under our care (about 20% of the population in the institution), it became mandatory for us to make a concentrated effort to educate them and evaluate and control their diabetic state as best we could. Here again a "teamwork approach" has proved far superior to relying on a physician to cope with the situation. Much is in store for the future of this project and its ultimate channeling into research on this subject. A committee of three consultants has been formed to oversee and plan a definite program for diabetics. Part of this plan has been the establishment of a fellowship in diabetes, with the appointment of a fellow to participate as an active research worker.

8. Psychological research: This was undertaken to determine the effects of certain drugs (Ritalin) on psychomotor responses. It proved good experience for the investigators for future experiments.

9. Rehabilitation of the senile: This has been one of the most fruitful projects at this institution. Under the guidance of one of the physicians and with an active team approach (social service, nursing, physical medicine departments), the results achieved in the management of these usually neglected patients have been very gratifying to all concerned. It can also be concluded that semi-senile and moderately senile patients do not have to be transferred to mental institutions, but can be adequately cared for in an institution such as ours.

Some of the projects we have in mind for the future include (1) a geriatric out-patient department; (2) a day centre for the benefit of older persons; and (3) a protective workshop.

EDUCATIONAL PROGRAM

All those taking part in the work of this institution as outlined above are automatically participating in a comprehensive program of education and self-education in geriatric medicine. The interns are given a better insight into the problems of the aged and what can and what cannot be done about them. The attending staff have the opportunity to act as clinicians and as consultants to patients with multiple chronic diseases and with long-term stay in the institution. We are certain that many of the attending physicians have changed their attitude and ideas regarding the care of the aged. A library with special emphasis on geriatric medicine is at the disposal of the medical staff in the institution.

The nursing staff and the orderlies have a sense of participation in a team by being included in some of the conferences and by a frequent series of lectures emphasizing our present-day concepts of the care of the aged.

Lectures given by various members of the staff to patients, residents and relatives have resulted in a better informed and more co-operative group, with ensuing all-round improvement in relations between them all and between them and the staff.

Two large groups of volunteers, viz., the Ladies' Auxiliary and the Men's Service Group, have proved of immense value through providing services and funds for the institution. The administration and the medical personnel meet these groups often to explain the medical and social program that is being carried out, and to elaborate on special facets of this program. These meetings have brought about an improved community spirit.

To stimulate the interest of the Toronto medical profession in geriatric medicine, an annual lectureship has been founded. An outstanding member of the profession or one who has made some major contribution to geriatric medicine is invited for this occasion. To date, these lectures have been most successful, as evidenced by the attendance and by the interest they have generated.

DISCUSSION

The increase in the span of life and the ever-increasing number of aged patients have gradually brought about a change of attitude towards the aged patient. Insulin has made it possible for many diabetics to live to a ripe old age. Because of the antibiotics, pneumonia in the aged is no longer looked upon as the "angel of death". A better understanding of the nature of diseases and of recuperative power in the aged and the improvement in techniques of surgery and anæsthesia have largely been responsible for the fact that old age *per se* is no longer a deterrent to surgical procedures. Mental and physical rehabilitation is now being increasingly emphasized, and we can and do rehabilitate some who were hitherto cast aside as hopeless and left to vegetate to the end of their days, to a healthier, happier and more meaningful life.

With all this in mind, when planning the medical program for Baycrest Hospital and the Jewish Home for the Aged, we set for ourselves two main objectives: first, to give our patients the best possible medical care—the type of care given in good general hospitals; and, second, to make our institution a centre for study, teaching and research in geriatric medicine. To attain these objectives it was considered essential to become affiliated with the New Mount Sinai Hospital. One very forceful reason for seeking this affiliation was our (C.A.M.) most frustrating experience as physician-in-charge of the medical services at the old Jewish Home for the Aged with its floor for chronically ill. Here the inadequacies of a volunteer medical service for patients in custodial care were only too apparent. It was difficult to obtain the number and type of doctors essential for adequate medical care. Those who did volunteer could not always be relied upon to come when required, and when they finally came they did not apply themselves as well as they should have. Perhaps the poor medical services were due to the meagre facilities and the uninviting, institution-type look of the old building. But now that we were going to have a new and modern institution with adequate facilities, we were determined to provide a medical service in keeping with present-day thinking. The day is long past when the aged could be looked upon as second-rate patients. Modern times demand a dynamic, comprehensive program for institutions such as ours.

It was also felt that, just as students and interns receive their training in pædiatrics in hospitals for sick children, so they could obtain training in geriatric medicine in modern, well-staffed and well-equipped homes for the aged.

Because the New Mount Sinai Hospital and Baycrest Hospital and the Jewish Home for the Aged were both new and modern institutions, the Medical Advisory Council of the New Mount Sinai Hospital and the lay executives and boards of both institutions accepted the challenge of a novel approach to the problems of the aged and agreed to this unique system of medical integration. It has to be stated that this program works to the mutual benefit of both New Mount Sinai Hospital and Baycrest Hospital and the Jewish Home for the Aged. As far as we are aware, the New Mount Sinai Hospital is the only general hospital (at least in this area) to offer its interns and medical staff this opportunity to participate in an organized clinical and educational program in geriatrics, and this thanks to the program of integration. To the best of our knowledge, this integration between a general hospital and a home for the aged and hospital for chronically ill is unique, and as it has been in operation for four years it is possible to assess its value. Because of old prejudices, there were at the outset, as was to be expected, much indifference and apathy among the doctors who served at Baycrest and in the Home. This has given way to a gradual but definite improvement in attitude and in quality of service on the part of everybody concerned, and we now feel justified in stating that our system of medical integration has proved itself successful and is here to stay.

Of the various factors responsible for this improvement, one must not overlook the increasing popularity of the study of senescence but, most important, our teaching program and various clinical and research activities, as outlined above, have created a lively interest among the members of the staff.

SUMMARY

In line with modern thinking about the care of the aged, particularly those in custodial care, Baycrest Hospital for the chronically ill and the Jewish Home for the Aged has developed a comprehensive program, which is presented in some detail.

Its distinctive and possibly unique feature is integration of its medical services with those of the New Mount Sinai Hospital. Service on a rotating basis at Baycrest is not only a responsibility of the staff of the New Mount Sinai Hospital, but also an opportunity to learn firsthand the problems and the disorders encountered in the aged.

After four years of operation the plan has been found to be workable and satisfactory, both for the patients and the staff.

Not only is our teaching and research program an added stimulus to the staff and a contribution towards change of attitude of doctors to their aged patients, but it also demonstrates what can be done in a well-equipped, well-staffed institution such as ours.

We wish to express our heartfelt thanks to the chiefs of departments at the New Mount Sinai Hospital and their respective staffs for their co-operation.

The executives, boards of directors and the administrators of both institutions have at all times given us encouragement and whole-hearted support, for which we are most grateful.

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PRIVATE PRACTICE

"Private Practice is playing the game of double or nothing right now. We who are closest to the system as participants must educate ourselves to demonstrate clearly that we mean private practice is for the public and not for ourselves. Nobody can do this for us and keep it private. If we believe in private practice, now is the time to prove it or before we know it, it will be gone."—H. M. Plaisted, *J. Maine M. A.*, 50: 84, 1959.

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SHORT COMMUNICATIONS

THE EVALUATION OF A COUGH SUPPRESSANT: AN EXERCISE IN CLINICAL PHARMACOLOGY*

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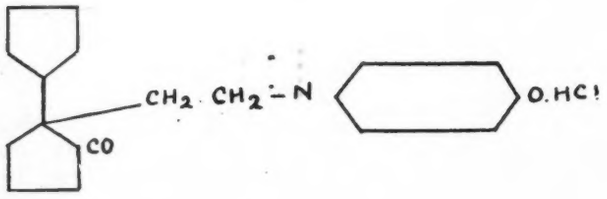
THE ASSESSMENT of the efficacy of an antitussive agent is subject to wide error, since cough is an extremely variable response to bronchopulmonary irritation, and as a rule does not lend itself to controlled study. Nevertheless, numerous methods[1-3] have been devised for the evaluation of antitussive agents and these have met with varying degrees of success. It is our firm opinion that the evaluation of a cough suppressant by its administration to a number of patients with chronic cough leaves much to be desired as an investigative technique. This was emphasized by one of us in a previous communication[4] on the evaluation of an antitussive agent by a controlled study of its effect on *induced* cough, a technique which is described below. The results of that study were later corroborated by Grégoire *et al.*,[5] using different methods.

The object of the present study was to determine the antitussive potency of a preparation, as yet unnamed, but referred to as *Preparation 10611* by its manufacturers. This preparation is described as 1-(β-N-morpholinoethyl)-1-cyclopentyl-cyclopentane 2-one hydrochloride and it has the following structural formula:



MATERIAL AND METHODS

The procedure followed was modified from that described by Bickerman and Barach[3] in 1954, and repeated by Shane *et al.*[4] in 1957. Solutions of citric acid in 10% and 15% concentration were nebulized in a Vaponefrin apparatus using oxygen at a flow rate of 10 litres per minute as a vehicle, and the inhalation of this citric acid aerosol was used to initiate the cough reflex. A Veeder-Root hand tally apparatus was used to count the resulting coughs.

A total of 65 volunteers who had been screened for the presence of spontaneous cough were further tested for tussive response to the citric acid aerosol and for cough suppression by codeine. Nineteen subjects whose cough reflex was not initiated by the citric acid aerosol inhalations and nine subjects whose cough reflex was not suppressed by half a grain of codeine were excluded from the study. Nine subjects were unable to complete the study for miscellaneous reasons. This left 28 patients who were considered suitable for study.

The first group to be completed (14 subjects) was tested with 15% citric acid aerosol, as this concentration had been reported by Shane *et al.*[4] to be a satisfactory cough stimulant. On 12 occasions each subject took five deep breaths of the nebulized material. The coughs occurring during the inhalation and for a five-minute period thereafter were counted and recorded. On three of these occasions no premedication was given; and ½ grain codeine and Preparation 10611, in doses of 25 and 50 mg. respectively, were each given on three separate occasions. All the tests were separated by at least 24 hours and all those involving medication were carried out an hour after the oral administration of the drug. The drug and control tests were not given in any detectable orderly sequence, and the subjects had no knowledge of the drugs or dosage that they were receiving at any given time.

Analysis of the data obtained from the first group (see Table I) indicated that the results, although statistically significant, were subject to wide variation and that there was no significant difference in the antitussive potency of 25-mg. and 50-mg. doses of Preparation 10611. Therefore, for the remainder of the study all suitable subjects were first screened with 10% citric acid aerosol; only when they failed to respond to this concentration on two separate occasions was the 15% aerosol used. No further tests were done with the 50-mg. dose of Preparation 10611.

The second group also consisted of 14 subjects, and the procedure was similar to that outlined for the first group with the two modifications described above.

RESULTS

Satisfactory results were obtained in both groups. There was a significant difference in response to the two strengths of citric acid aerosol. Although 10% citric acid aerosol initiated a milder response than the 15% solution, as measured by the number of coughs induced, there was still a wide variation in response. The results obtained in both groups are statistically significant and are presented in tabular form in Tables I and II. The significance of the results is apparent from the statistical data appended to these tables.

It is evident from Table I that codeine grain ½ (30 mg.) and Preparation 10611 in doses of 25 and 50 mg. will suppress the cough reflex as induced by 15% citric acid aerosol to approximately 50% of the premedication response. Two conclusions can be drawn from this fact: (1) that Preparation 10611 has an antitussive action equivalent to that of codeine mg. for mg.; and (2) that

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This study was carried out with the aid of a grant from Ciba Co. under the auspices of the Dalhousie Postgraduate Committee.

TABLE I.—ANTITUSSIVE EFFECT OF PREPARATION 10611 ON COUGH INDUCED BY THE INHALATION OF 15% CITRIC ACID—COMPARED WITH CODEINE

	A. Without sedation				*B. Codeine grain 1/2*				*C. 10611, 25 mg.*				*D. 10611, 50 mg.*			
	No. of coughs				*No. of coughs*				*No. of coughs*				*No. of coughs*			
Tests	*1*	*2*	*3*	*Mean*	*1*	*2*	*3*	*Mean*	*1*	*2*	*3*	*Mean*	*1*	*2*	*3*	*Mean*
1. D.B.	16	12	12	13.3	0	9	0	3.0	0	0	0	0	0	0	0	0
2. T.B.	13	14	8	11.7	11	11	6	9.3	9	11	6	8.7	11	7	4	7.3
3. J.B.	5	17	7	9.7	0	1	0	0.3	0	0	0	0	1	0	0	0.3
4. S.G.	38	29	21	29.3	35	15	3	16.7	22	16	8	15.3	8	6	2	5.3
5. P.G.	4	5	0	3.0	1	1	0	0.7	0	4	0	1.3	1	0	0	0.3
6. D.J.	27	30	26	27.7	21	19	10	16.7	15	12	11	12.7	14	12	10	12.0
7. R.M.	17	21	15	17.7	14	9	11	11.3	14	8	10	10.7	14	9	11	11.3
8. M.M.	16	9	4	9.7	7	8	2	5.7	2	0	0	0.7	1	0	0	0.3
9. B.O.	21	14	30	21.7	21	10	2	11.0	16	7	4	9.0	12	21	6	13.0
10. V.P.	32	18	19	23.0	11	13	18	14.0	13	13	18	12.7	18	18	18	18.0
11. B.S.	25	18	15	19.3	5	0	12	5.7	12	7	21	13.3	2	18	24	14.7
12. H.T.	16	16	14	15.3	1	0	2	1.0	12	10	13	11.7	8	15	11	11.3
13. R.W.	29	34	18	27.0	16	9	10	11.7	15	12	8	11.2	16	11	9	12.0
14. M.W.	19	20	15	18.0	13	6	0	6.3	0	1	9	3.3	13	9	9	10.3
Group Mean				17.3				8.1				8.1				8.3
S.D.*				8.2				7.2				6.5				6.8
S.E.M.**				1.26				1.11				1.00				1.04

Significance of differences between means:

Means compared	S.E.D.***	t†	P††
1. A and B	1.64	5.69	Less than 0.001
2. A and C	1.60	5.75	Less than 0.001
3. A and D	1.63	5.52	Less than 0.001
4. B and C	1.49	0.0	Greater than 0.9
5. B and D	1.51	0.13	Greater than 0.8
6. C and D	1.44	0.13	Greater than 0.8

*S.D. = Standard deviation.
**S.E.M. = Standard error of the mean.
***S.E.D. = Standard error of the difference.
†t = Difference between means / Standard error of difference
††P = Probability of difference being due to chance alone.

there is no increase in antitussive potency as the dose is increased beyond 25 mg.

Table II reveals that, when a milder stimulus is used to induce the cough reflex, codeine grain ½ and Preparation 10611 (25 mg.) both suppress the response to approximately 35% of the premedication level. It is again apparent that codeine and Preparation 10611 exert an antitussive action that is almost exactly equivalent milligram for milligram.

There were no important side reactions to either the citric acid aerosol inhalations or to Preparation 10611.

CONCLUSIONS

The method of evaluating antitussive agents by their suppressive effect on cough induced by citric acid aerosol has again been found to be satisfactory,

TABLE II.—ANTITUSSIVE EFFECT OF PREPARATION 10611 ON COUGH INDUCED BY THE INHALATION OF 10% AND 15% CITRIC ACID—COMPARED WITH CODEINE

	A. Without sedation				*B. Codeine grain 1/2*				*C. 10611, 25 mg.*			
	No. of coughs				*No. of coughs*				*No. of coughs*			
Tests	*1*	*2*	*3*	*Mean*	*1*	*2*	*3*	*Mean*	*1*	*2*	*3*	*Mean*
1. B.A.	12	10	4	8.7	4	2	2	2.7	5	5	4	4.7
2. E.B.	8	9	10	9.0	5	5	3	4.3	4	2	5	3.7
3. A.C.	28	15	8	17.0	13	4	6	7.7	10	7	3	6.7
4. M.D.	7	13	6	8.7	0	10	7	5.7	0	5	6	3.7
5. J.D.	6	10	7	7.7	0	0	0	0.0	4	1	2	2.3
6. J.L.	9	10	15	11.3	1	0	0	0.3	0	0	2	0.7
7. O.M.	4	6	9	6.3	0	1	0	0.3	2	4	3	3.0
8. W.M.	6	9	8	7.7	0	2	0	0.7	3	2	1	2.0
9. C.P.	6	3	6	5.0	2	4	3	3.0	0	4	3	2.3
10. A.R.	15	14	4	11.0	13	6	6	8.3	9	8	7	8.0
11. M.T.	3	0	9	4.0	0	0	0	0.0	1	0	0	0.3
12. C.W.	9	8	4	7.0	8	8	3	6.3	4	4	6	4.7
13. D.W.	3	8	1	4.0	0	0	0	0.0	4	0	1	1.7
14. E.W.	21	25	21	22.3	7	1	8	5.3	15	0	4	6.3
Group Mean				9.3				3.2				3.6
S.D.*				5.2				3.5				3.1
S.E.M.**				0.89				0.48				0.42

Significance of differences between means:

Means compared	S.E.D.***	t†	P††
1. A and B	1.01	6.03	Less than 0.001
2. A and C	0.98	5.81	Less than 0.001
3. B and C	0.63	0.63	Greater than 0.5

*S.D. = Standard deviation.
**S.E.M. = Standard error of the mean.
***S.E.D. = Standard error of the difference.
†t = Difference between means / Standard error of difference
††P = Probability of difference being due to chance alone.

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providing statistically significant, reproducible and meaningful results.

Preparation 10611 has a suppressive effect on induced cough almost exactly equivalent to that of codeine, milligram for milligram.

There is no increase in the antitussive action of Preparation 10611 when the dose is increased from 25 mg. to 50 mg.

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EFFECT OF NICOTINIC ACID ON LIVER FUNCTION AND LEUKOCYTES*

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INTRODUCTION

NICOTINIC ACID lowers the cholesterol content of serum when fed to rabbits[1] and human subjects,[2-5, 7, 9, 10] and this effect is maintained during medication. However, the cholesterol levels return to their pre-treatment levels within a few days after the treatment is discontinued.

It is, therefore, feasible to test the hypotheses whether or not lowering cholesterol levels will have a beneficial effect on the arteriosclerotic individual, either by inhibiting further development or even by allowing reparative processes to reverse some of the changes already present.

This method of lowering cholesterol levels has the advantage of simplicity, effectiveness, minimal interference with dietary habits and relative safety. The safety of using nicotinic acid in the recommended dosages is suggested by a great deal of investigative research over the past two decades. Most authors have failed to find toxic changes. Altschul and Hoffer[5] found several reports of apparent toxicity but these were due to the amount of hydrogen ion (acid) consumed rather than the vitamin. Handler and Dann[6] reported that 2% nicotinic acid (equivalent to 154 g. per day per 70-kg. man) in the diet produced fatty liver in rats but they did not report any microscopic evidence. Altschul in the report by Altschul and Hoffer[5] could not find evidence for fatty liver degeneration when he duplicated the study of Handler and Dann.[6] In addition, nicotinic acid has been used in these dosages as a treatment of schizophrenia,[7] and there has been no clinical evidence for toxicity in up to four years of continuous medication.

The present report concerns more recent studies of the effects of chronic administration of nicotinic acid upon liver function and on leukocytes.

MATERIAL AND METHODS

Twelve patients, most of them schizophrenics who had responded well to treatment, were given a bromsulphalein test. They had been on treatment (3 grams/day) for at least one year, and the mean duration of treatment was 2.6 years.

Another group of 36 (chiefly schizophrenic patients) was given 3 g. per day of nicotinic acid for 30 days. Leukocyte counts were made just before and just after this period.

RESULTS

The bromsulphalein test results are given in Table I.

TABLE I.—EFFECT OF NICOTINIC ACID ON LIVER FUNCTION

Subject	*Duration of treatment years*	*Sex*	*Age*	*Bromsulphalein retention—%*
1	2	F	52	18.0
2	3	F	28	11.5
3	3	F	38	1.5
4	2	F	37	2.0
5	1.25*	F	52	1.5
6	3 *	M	36	3.0
7	4	F	33	2.0
8	2	M	39	1.0
9	3	F	45	2.0
10	2.5	F	36	4.0
11	1 *	F	46	2.0
12	4	M	56	1.0
Mean	2.6	—	—	4.1

*Not taking nicotinic acid during test.

All other patients were on medication during test. Bromsulphalein results are expressed as retention of dye using 5 mg./kg. 45 minutes after injection.

Of the group of 12, only the first two yielded abnormal results. Both patients were chronically ill schizophrenic patients before treatment started. Since a small proportion of schizophrenic patients have abnormal liver function tests, it is likely that these abnormal results were due to a schizophrenic factor rather than to the nicotinic acid. The mean retention of dye was well within normal limits for the group.

The effect of nicotinic acid upon leukocyte count is shown in Tables II and III.

There were no significant changes in these values.

*Research supported by Public Health Grants, Ottawa, and the Rockefeller Foundation, New York, under the auspices of the Saskatchewan Committee on Schizophrenia Research.

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TABLE II.—EFFECT OF NICOTINIC ACID ON LEUKOCYTES

	Before medication				*After medication*			
Subject	*Total W.B.C.*	*Lymphocytes*	*Neutrophils*	*Eosinophils*	*Total W.B.C.*	*Lymphocytes*	*Neutrophils*	*Eosinophils*
1	7850	1884	5574	55	4700	1410	3008	55
2	6650	1131	4988	96	6500	1430	3965	143
3	12800	2304	9472	181	6300	1197	4652	163
4	4000	1320	2560	18	4600	1288	2944	37
5	5800	2436	2668	187	7550	2643	3926	407
6	7650	2907	4437	129	9700	3492	5626	116
7	8600	2580	5676	251	11550	3350	7854	176
8	9600	2880	6048	99	12400	2232	9424	77
9	13400	3216	9380	347	12200	2440	8052	649
10	8150	2282	5053	193	10400	2184	7592	40
11	10150	3350	6395	113	6800	2856	3876	76
12	9300	1860	6696	216	7300	1241	5694	26
13	9450	1229	6143	1327	10650	1278	5858	2416
14	6900	2139	4071	50	6400	2304	3904	120
15	6350	2604	3175	90	8100	2835	3483	180
16	5250	1155	3780	77	4900	1470	3234	66
17	5250	1943	3150	66	4600	1334	3174	33
18	7050	2045	4935	22	6100	1281	4575	176
19	7850	3219	3768	385	10000	1300	8000	77
20	9200	2208	6440	77	10000	2500	7400	187
21	6900	2346	4140	132	8600	2494	5332	77
22	6150	1784	3690	191	5450	3161	1690	121
23	8000	2720	4720	53	7850	2120	5181	77
24	8600	2838	5074	176	6300	2142	3717	113
25	8350	2255	4927	165	10250	3075	6355	130
26	7400	2368	4292	85	7950	2544	4770	90
27	6350	1651	3937	53	5200	8884	4004	76
28	5900	1475	4012	143	4700	1974	2162	81
29	5500	1320	3740	62	4800	1680	2832	75
30	5850	1872	3510	130	6400	1856	4096	142
31	8600	2838	5246	181	8600	3096	5074	130
32	7600	1976	4180	890	5150	2112	2833	77
33	9050	1991	6607	264	7600	1824	4864	319
34	8750	2188	5425	937	9800	2156	6468	715
35	7050	1904	4865	110	5000	1050	3750	176
36	5950	2678	2975	100	6950	2433	4240	312
Mean	7716	2192	4882	212	7538	2074	4823	221

TABLE III.—EFFECT OF NICOTINIC ACID ON LEUKOCYTE COUNT DURING MEDICATION

	Before				*During*			
Subjects	*Total*	*Lymphocytes*	*Neutrophils*	*Eosinophils*	*Total*	*Lymphocytes*	*Neutrophils*	*Eosinophils*
1	6200	1550	4216	103	7700	1078	5775	48
2	9700	2522	5820	263	7350	2426	4263	445
3	7350	3381	3234	53	4700	2961	1645	53
4	13950	3069	9765	209	9500	3515	5700	66
5	8350	3674	4175	53	7500	2550	4575	78
Mean	9110	2839	5442	136	7350	2506	4392	138

Thus the evidence confirms the safety of administering nicotinic acid over long periods of time. Altschul and Hoffer[5] discussed the acidity of this preparation as an irritant and showed that when buffered with sodium bicarbonate this irritant effect was removed while retaining the effect on cholesterol.

CONCLUSION

Nicotinic acid in dosages of 3 grams per day administered over a period of two years produced no liver damage. Over a 30-day period, there was no change in leukocyte count.

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THE HEALING ART AND THE COLLECTIVE MIND

In Canada, there is still a widespread belief that the opinion of those who have studied and practised a subject is on the whole worth more than that of the self-appointed experts with no particular training. This belief is by no means universal, however, and some of us view with dismay the continuing encroachments of unreason into the scientific field. But this dismay deepens when we contemplate the medical scene in some other parts of the world and witness the sweeping away of the concept that 2 and 2 make 4, whatever the political colour of the government.

A particularly interesting example of this trend is to be found in the *Chinese Medical Journal* for November 1958, in which great importance is given to an article entitled "The Fight to Save Steel Worker Ch'iu Ts'ai-K'ang's Life". This unfortunate patient was burned by molten steel and it is alleged that he received an 89.3% body surface burn, with 20% third-degree burn. According to the world literature, say the editors, there was little or no hope for him. But, they add, "when politics take the lead over scientific theory, when specialists cease in their blind worship of established authority, then miracles can happen". The process leading to the saving of his life is described as a process of grave and intense struggle between the proletarian and bourgeois medical conceptions and between proletarian and bourgeois therapeutic methods.

When the doctors shook their heads and gave an unfavourable prognosis they were told by the Party Committee of the Shanghai Second Medical College not to be silly. The Committee analyzed their ideological state and "correctly pointed out that what could not be done in capitalist countries could be done in China". Galvanized into activity by the stern words of the Party Secretary, the doctors "quickly passed over from a state of stupor into a state of activity", covering the world literature on burns in one morning and deciding on 15 alternative methods of treatment. The main problem appeared to be the treatment of a *Pseudomonas pyocyanea* bacteræmia, which was controlled by polymyxin and bacteriophage. The phage was obtained as a joint effort by 60 students from the College who combed the rural areas every day for days, bringing back samples of fæces and sewage water for isolation and culture until the necessary phage was obtained.

Over the question of skin grafts, the doctors were also persuaded to see the error of their ways and to graft the patient's wounds many days earlier than normally would have been done. One valuable facet of the treatment seems to have been that all sorts of departments were called in for consultation, including the departments of dermatology, surgery, internal medicine, urology and even pædiatrics (to remind their colleagues of the suitability of scalp veins for infusion). Not only this of course but the overall guidance of the Party, who led the doctors forward step by step, had a decisive effect on the result. We can best summarize the tension between the Party and the doctors by the following quotation:

"'Can everybody treat diseases?' one doctor asked. 'My bit of knowledge took me twenty years of hard work to accumulate.' Behind this lurk unmeasurable arrogance, self-conceit and detachment from reality.

"'The curing of disease cannot be hurried,' another said. 'How fast the course runs is beyond our control. In medical work, you just can't apply the more and faster stipulated in the General Line.' Such self-abasement and disregard of the latent potentialities in Man are actually a desire to go to sleep in an easy chair and wake up in a ready-made communist society."

The whole story raises an interesting series of speculations. First of all, the patient got better, and the editors obviously believe that this was due to the activities of the Party. Maybe there is a grain of truth in this belief; maybe the medical staff were not bending all their energies to saving Comrade Ch'iu's life, and only the mobilization of all forces achieved this. But the alarming feature of the case is the suggestion that wound healing and wound infection can be different in different political settings. The logical conclusion of this would be that, every time the government of Canada changed, we should have to re-write the pharmacology texts in accordance with Conservative or Liberal therapy. Heaven forbid, for prescribing is already complicated enough without this additional hazard.

Editorial Comments

ETIOLOGY OF THE LEUKÆMIAS

A recent issue of the Soviet journal, *Klinicheskaia Medicina* (No. 7, July 1958), is devoted to the leukæmias and other blood dyscrasias, thus paying homage to the foremost hæmatologist of the U.S.S.R., Professor I. A. Kassirsky, on the occasion

of his 60th birthday. In the editorial, Markov notes that whilst western scientists are tending to concentrate on radiation and virus infection as etiological factors in leukæmia, Soviet scientists are actively engaged in clarifying endogenous factors in the etiology and pathogenesis of these diseases. The increased incidence of leukæmia observed in many countries over the past 30 years is also evident in the Soviet Union, though not quite to the same degree. It is highest in the Baltic countries and lowest in the Asiatic republics. In Moscow in the period 1945-1950, 251 cases of acute leukæmia or 0.65% and 140 of chronic leukæmia or 0.37% were found among the 38,367 autopsies performed in six institutes. In the following five years the percentages rose to 1.86 and 0.94 respectively.

Kassirsky reviews current theories on the etiology of leukæmias and reminds us that, whilst radiation has undoubtedly caused some cases of leukæmia, the overwhelming majority of cases are in no way connected with this factor. Even solar and ionizing radiation can be dismissed as a contributory cause, especially as this is contradicted by the observation of an increased incidence of leukæmia in the northern parts as against the southern regions of the U.S.S.R. He cites the experimental evidence of a high incidence of leukæmia in certain mouse colonies and the recently growing interest in familial occurrence of leukæmia in humans to underscore the importance of endogenous factors. Although experimental evidence seems to support the virus infection theory, the relationship is only apparent and not real. Against it is the lack of even a single case of human leukæmia acquired by transmission in surgeons or physicians handling leukæmic material or in patients after receiving transfusions of leukæmic blood accidentally or in the therapy of agranulocytosis. He quotes the work of Kasjansky as definitely disproving the occurrence of epidemic leukæmia in chicks. According to Kassirsky, the material which transmits leukæmia in experimental animals is a chemical rather than a virus. It is not only an ultrafiltrate but is also resistant to formalin and glycerin in contradistinction to viruses; thus it is an inanimate essential cell metabolite. Kassirsky believes that the organules of the cytoplasm acquire abnormal properties through mutation, and that this abnormality takes some time to become apparent or else that the organism is able to contain them for some time through neutralizing metabolic antifactors, such as are now considered to be present in other neoplastic conditions. He supposes that the nucleus of every cell contains a proliferating and a differentiating factor and that normally the micro-products liberated on destruction of blood corpuscles help to inhibit the action of nuclease, which is to destroy the differentiating factor in cells. If however there is a congenital defect in the nucleotide system or if damage is produced by exogenous agents (such as radiation, whose chromosomal action is well known), there may come about a gradual exhaustion of the deficient factor, and if this is the differentiator there will be a predominance of the proliferating factor. This theory does not imply that he has taken the attitude of genetic fatalism, continues Kassirsky. As a determinist he accepts facts and their causation as real things, and the emphasis on the role of genetic factors does not contradict the materialistic conception of natural sciences and of medicine as to the unity of environment and organism. This latter formula has at times been interpreted with too much emphasis on the environment, without due regard for inherited and acquired (through mutation) properties of the organism.

Regarding future development in the treatment of leukæmias, Kassirsky mentions the work of Timofeyevsky and Benevolenskaya, who have been able to cause maturation of leukæmic myeloblasts in tissue cultures by adding mature leukocytes. The beneficial effects of pyogenic processes elsewhere in the body on the leukæmic disorder require further elucidation, and the efforts of biochemists should be directed to discovery of the unknown factors present in the body during a remission brought about by this or some other means. Perhaps one should look for metabolic products acting as biological antagonists—antibiotics of the leukæmic process, so to speak. Although the sera of Bogomoletz, Raushenbach and Osechenskaya (antiblastoma serum) as well as some others have not been successful, possibly because they were not sufficiently specific, there is need to explore this field more intensively with a view to isolating the antigenic properties of the virus-like organules and producing antifactors through inoculation of suitable animals.

Reinberg, a radiologist, reviews the relationship between ionizing radiation and leukæmia. Although he personally has never seen a case in which leukæmia has developed after exposure to x-rays, he accepts the evidence of other authors as proving the increased incidence of leukæmia in people exposed to excessive x-ray examinations. As regards the increasing danger to the human race from the rising atmospheric content in ionizing radiation due to atomic explosions, he believes that this is real and requires concerted action for control. There is a need to establish international norms for maximum safe dosage of radiation; most important of all, it is urgent that all atomic bomb tests be discontinued without delay.

W. GROBIN

TETANUS

Statistical studies indicating the dramatic reduction in the incidence of tetanus after the general issue of antitoxin in the early days of World War I speak for the efficiency of this drug. As a result of a subsequent attitude almost amounting to complacency, relatively little attention has been paid to this often fatal disease in the intervening years. In recent literature, however, articles are again appearing to remind us that with a little more cognizance of the problems, the mortality may be even further reduced.

In one of these papers, Professor Payling Wright[1] reminds us of the progressive loss of immunizing power of antitoxin that results when one inoculation of serum follows another. That is to say, a supposedly prophylactic inoculation after an accident may fail because an injection some months previously may have induced an immunity to horse serum with consequent accelerated destruction of

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the specific serum globulins. Thus, as Littlewood, Mant and Wright[2] advocated in 1954, "Once a person has received an injection of any horse serum antitoxin, irrespective of the disease for which it may have been given, that person should be promptly immunized against diphtheria and tetanus with the appropriate toxoid. By thus creating the state of active immunity, which can be effected without any unpleasant side effects, any future need for passive protection against these diseases with horse serum antitoxin is rendered unnecessary. Furthermore, before any surgical measures are undertaken on tissues which have been previously traumatized and may in consequence harbour contaminating tetanus spores, active immunization should always be carried out beforehand."

In addition to dying from convulsions, patients may of course die as the result of over-enthusiastic use of drugs, so that in addition to finding a suitable drug the pharmacological action must be studied to determine the correct dosage. Ideally, such a drug should abolish tetanus convulsions but not depress respiration or consciousness to an appreciable degree.

There is a tendency to be too optimistic about the results being obtained with current forms of therapy, for if one selects the most severely affected patients, very little improvement in the mortality rate will be found. It is a disease in which many variables enter the picture. Of these the "period of onset"—that is, the time between the first symptoms of tetanus and the first reflex spasm—seems to be the most important index of severity and prognosis. It is now considered to be more reliable than the incubation period. It is only by taking all these variables into consideration and carefully analyzing large series of cases that the best forms of therapy can be decided upon.

Professor Adams,[3] basing his opinion on a study of 200 cases in Durban, came to the conclusion that no definite reduction of the mortality rate has followed the introduction of chlorpromazine for the treatment of tetanus when compared with sedation methods previously used. Similarly, Creech *et al.*,[4] in 1957, had the same impressions, although they did note that a steady decline had taken place in this mortality rate in their New Orleans hospital in the preceding 50 years.

Early diagnosis is imperative, so that specific steps can be taken to halt the progression of the disease and provide adequate supportive therapy during its self-limited course. Primary consideration must be given to neutralization of any circulating toxin before it can combine with the central nervous system and produce further effects. The focus of infection must then be eradicated to prevent further production of toxin. This is attempted by radical surgical excision and combined penicillin and streptomycin therapy.

These preliminary steps having been taken, control of the reflex muscle spasms with concomitant maintenance of pulmonary ventilation must follow, as the majority of deaths from tetanus are due to inadequate or improper control of these spasms and the secondary effects of hypoventilation. Some of these severe cases will respond only by paralyzing the patient completely with curare and maintaining intermittent pressure respiration through a tracheotomy. As a decreased thoracic compliance is responsible for the inefficiency of ventilation in tetanus, it is wise to alternate positive with negative pressure. In order to facilitate filling of the right side of the heart, the period of expiration should be of longer duration than inspiration.

Crandell[5] maintains that muscle relaxants that act centrally by depressing the polysynaptic neuronal transmission have a more specific and logical pharmacological action. He advocates methocarbamol, either orally or intravenously, in a 2.5% isotonic solution. In addition, he uses barbiturates to produce psychic sedation. Chlorpromazine is employed to potentiate the action of the other two. Previously it had been demonstrated by Brooks *et al.*[6] that tetanus toxin selectively affects the interneurones of polysynaptic reflex arcs in the central nervous system by suppressing inhibitory synaptic action.

In spite of these newer methods, constant vigilance and expert nursing care remain of paramount importance. The need for early tracheotomy and maintenance of a clear airway is obvious. The insertion of a Levin tube, or even performance of a gastrostomy, will reduce the hazard of regurgitation and aspiration. Attention to fluid and electrolyte balance must not be forgotten. Frequent aspiration of the chest and turning from side to side are mandatory to prevent pneumonic congestion or decubitus ulcer formation. Last but not least, the nutritional requirements must not be forgotten as the weeks pass by.

Reflection on the still high mortality rate, or even the prolonged morbidity of this condition, should be sufficient impetus for progress of active immunization in all civilians, especially children, as well as service personnel.

ALLAN M. DAVIDSON

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BARIUM ENEMA TREATMENT OF INTUSSUSCEPTION

The basic work on the use of hydrostatic pressure in the reduction of barium enema was carried out by Hirschsprung of Sweden, and Mark M. Ravitch has been its leading exponent in the United States. Since 1950, hydrostatic pressure reduction of intussusception by barium enema under fluoroscopic control has been the treatment of choice at the Johns Hopkins Hospital, and no case has been fatal since 1946.

Ravitch, who has recently analyzed 77 cases (*New England J. Med.*, 259: 1058, 1958), believes that a barium enema can and should be administered to every child with intussusception, regardless of the duration of the disease.

Once the diagnosis is suspected, the operating room is notified. Intravenous infusions of fluids are started at once, the stomach is emptied and a gastric tube is left in place. In the fluoroscopy room

an ungreased 45 ml. Foley-bag catheter is inserted into the rectum, the balloon is inflated and the buttocks are carefully strapped together with adhesive. The catheter is connected to an ample reservoir of barium at a height of between 3 and 3½ ft. (90-105 cm.) above the table. Anæsthesia is not used, and the barium is allowed to run in without interruption. If at any time the barium is delayed absolutely for 10 to 15 minutes, the procedure should be abandoned. Manual pressure on the abdomen must not be employed, and the canister must not be raised higher than 3½ ft. above the table. If these precautions are followed, perforation of gangrene of the bowel will not occur. Ravitch makes the point that the surgeon must perform the treatment. If the ileum does not fill freely, operation should be carried out at once.

In this series, 69% of the cases were reduced by barium enema alone. At operation, additional cases were found to be reduced, thereby raising the percentage of reduction by barium enema to 75%. Only one case in the series required a bowel resection. Several of the irreducible cases were associated with a Meckel's diverticulum.

After the reduction is completed, powdered charcoal is deposited through the gastric tube, and six hours later an enema is given to recover the charcoal and confirm the success of reduction.

The successful reduction of an intussusception is indicated by the following criteria: the entrance of barium well into the small bowel; the return of the barium with fæces or with flatus; disappearance of the mass; clinical improvement of the child and subsequent recovery of the charcoal in the stool, or the appearance of a blood-free stool.

The advantages of such a program are obvious. Risk of postoperative obstruction is abolished in 75% of the cases. In the cases that require operation a McBurney incision is used, and this may decrease the operating time and the incidence of postoperative obstruction.

Many surgeons still feel, however, that operation is more certain than hydrostatic reduction. For those with limited experience in management of this disease, this would seem to be true. It would also seem wise for the surgeon to enlist the help of the radiologist rather than to antagonize him by carrying out a barium enema study in his department.

T. A. MACLENNAN

THE CARE OF THE AGED

Public and professional interest in the elderly population is increasing, and this is being made more apparent through establishment of special sections for geriatrics in medical associations, and the publication of journals devoted to this branch of medicine. Efforts are being made to improve the services in nursing homes, which are rapidly increasing in numbers, and to standardize the various institutions serving our aged citizens. There is an obvious need to ensure that the residents are protected financially, are given adequate nursing, and most of all that they are housed in homes not likely to become death-traps in fires.

The most obvious reason for this great interest in the aged lies in the ever-increasing numbers reaching and surpassing the age of seventy. Dr. Wittson, speaking before the A.M.A. Planning Conference on Aging last year, pointed out that old age has an incidence of 100 per cent among the living populations, and that when doctors plan a healthy future for the aged they are planning it also for themselves.

In a recent issue of the *Journal of the American Medical Association*, two different types of designs for living for the aged are described (169: 146 and 149, 1959). The Mary Manning Walsh Home in Manhattan is operated by the Carmelite Sisters, and its 300 residents are involved in an amazing variety of activities, leaving them little time for self-pity. They are free to come and go as they please, and many of them have discovered new interests in life since entering the institution. Every effort is made to remove the stigmata of old-time institutions from this "hotel for the elderly". A "village" for the aged was developed by the Good Samaritan Society, a Lutheran group, in an outlying district of Hastings, Nebraska. This community was established in 1958, and has both small apartments for those who can maintain their own households and rest homes for those who need help with feeding, dressing and walking.

In Toronto, the Jewish Home for the Aged and its hospital for chronically ill moved into its new quarters over four years ago. The outstanding features of this Home are integration of the medical services with those of a general hospital, the New Mount Sinai Hospital. A visit to this institution is a stimulating experience, and it is not hard to see the reasons for its success. Nor is it too much to expect that valuable knowledge will be acquired by the medical staff, who are engaged in various research projects. The details of these as well as other features of the Jewish Home for the Aged are described elsewhere in this issue (p. 730). Is it merely accidental that these three successful attempts at solving problems of care of the aged were initiated by organizations with strong religious affiliations? To this writer, this fact indicates that religions are not merely spreading charity but are fully aware of the social problems of our present society.

ASSOCIATION NOTICE

The sessions of the Ninety-First Annual Meeting of The Canadian Medical Association will be held as follows:

(a) The meeting of the General Council will be held on Friday and Saturday, May 29 and 30, 1959, in the Royal York Hotel, Toronto.

(b) The Annual General Meeting for the installation of the President will be held at 11.00 a.m. on Tuesday, June 30, 1959, in the Royal York Hotel, Toronto.

(c) The Scientific Sessions will be held jointly with those of the British Medical Association in Edinburgh, July 18-24, 1959.

All of the above constitute the Ninety-First Annual Meeting of The Canadian Medical Association.

A. D. KELLY, M.B.,
General Secretary.

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THE INSTALLATION OF THE PRESIDENT

All members of The Canadian Medical Association and their wives are invited to attend the Annual General Meeting and Association Luncheon to be held at the Royal York Hotel, Toronto, on Tuesday, June 30, 1959.

The Annual General Meeting will be convened at 11.00 a.m. in the Concert Hall of the Royal York Hotel for the purpose of installing His Royal Highness, Prince Philip, Duke of Edinburgh in the office of President of The Canadian Medical Association. The ceremonial installation will be followed by an Association Luncheon in the Canadian Room at which our royal President will preside.

The occasion is unique in that for the first time The Association has been honoured by the election of a royal personage to our highest office. It is our hope that, following the dignified ritual of installation, the informal atmosphere of a medical family party will prevail. The order of dress is summer frocks, with hats, for ladies and business suits for men.

Although the capacities of the Canadian Room and the Concert Hall are very large, they are not unlimited, and places for both portions of this function will be reserved up to capacity in the order in which they are received. The form below should be used to order tickets at the price of $5.00 each.

The General Secretary,
The Canadian Medical Association,
150 St. George Street,
Toronto 5, Ontario.

Please send me.....tickets at $5.00 for the Annual General Meeting and Association Luncheon in the Royal York Hotel, Toronto, on Tuesday, June 30, 1959. I attach my cheque in the amount of $.....

Places will be occupied by.....

.....

.....

.....

Name of member (please print).....

Address.....

Medical News in brief

NEONATAL INFECTIONS IN A COMMUNITY HOSPITAL

Two outbreaks of neonatal infection in the nursery of a community hospital of 300 beds are reported by Van Gelder *et al.*, (*J. A. M. A.*, 169; 559, 1959). The first outbreak was associated with *Listeria monocytogenes* and was fatal to 3 out of the 4 children involved. The second, a year later, involved 26 children of whom 9 died. In this case the organisms were mainly Group A streptococci.

The authors emphasize that overcrowding was a striking factor in both nursery outbreaks, and plead for the help of hospital planners and architects in maintaining a fixed ratio of bassinets to post-partum beds. They also mention once more the various consequences of not having a medical staff organization with power to carry out a thorough investigation of an outbreak and to take immediate protective steps. They observed that the most common symptom in the second outbreak was a change in the infant, such as development of anorexia, apathy or irritability. They speculate on the frequency with which cardiac failure occurred; it is possible that a virus was associated with the bacterial infections and led to the myocarditis.

They also stress once more the failure of some of the patients to respond to antibiotics, and draw attention to the false sense of security which antibiotics now impart, as well as their masking effect in preventing isolation of causative organisms. Another feature of the epidemics was the common presence of umbilical infection; it might be wise to use dressings and the daily application of antiseptics to the cord and the surrounding skin to reduce such infectivity.

A NEW ANDROGEN FOR ADVANCED BREAST CANCER

Although androgenic hormones induce temporary regression of lesions in patients with metastatic carcinoma of the breast, the regressions are not constant and are of relatively short duration. In an attempt to enhance the anti-cancer effect of testosterone, various alterations in its structure have been made, and Blackburn and Childs of the Mayo Clinic (*Proc. Staff Meet. Mayo Clin.*, 34: 113, 1959) report some promising results with a new derivative called 2-methyl dihydrotestosterone. They compared the effects of this androgen with testosterone propionate, giving each drug intramuscularly as its propionate ester at a dose level of 100 mg. three times a week. All the 48 patients studied were postmenopausal women with metastatic carcinoma of the breast and objective evidence of progression of the lesions.

The authors observed temporary regression of metastatic lesions in three out of 21 patients given testosterone and in 12 out of 27 patients given 2-methyl dihydrotestosterone. Thus it appears that the new androgen has an inhibitory effect at least equal to and probably superior to that of testosterone, although the androgenic effect of the new derivative seems to be less.

BULLOUS PNEUMONIA IN INFANCY

In 1952 the French pædiatrician Debré described a clinical syndrome in small children characterized by an x-ray picture of numerous cysts, containing air and of variable and changing size, in the lung of an infant with a staphylococcal infection. Although many publications have since appeared in France, Germany, Italy and Scandinavia, practically no attention has been paid to these findings in the United States or in Canada.

Tremblay and his colleagues from Chicoutimi (*Laval méd.*, 27: 157, 1959) now report six cases of this interesting clinical condition. The malady is ushered in by a variable phase of infection, with dyspnœa as the important and sometimes the only symptom. This is followed by a second phase in which the child's general state is changed for the worse and physical signs are variable, but the radiological picture is characteristic. In one of the lung fields, there are a number of bullæ whose size and number change repeatedly. They may occupy the whole hemithorax and persist for several weeks or months, during which they diminish in volume and finally disappear.

The infant may either get better or die in asphyxia with rapid expansion of bullæ, or the condition may become complicated by a pneumothorax, pyopneumothorax or empyema. It may be difficult to obtain a culture of the causative organism, the *Staphylococcus aureus*.

Treatment is in the first instance by antibiotics. Chloramphenicol and the tetracyclines are effective, and so is streptomycin despite the rapid development of resistance. Erythromycin and rovamycin have given satisfactory results also.

URINARY PROTEOSE IN RENAL DISEASE

Analyses of urine from a patient with active glomerulonephritis suggested the presence in the urine of a heat-resistant, water-soluble substance, protein-like in nature. Levine and his colleagues from Chicago (*J. Lab. & Clin. Med.*, 53: 167, 1959) report how, starting with this observation, they succeeded in isolating a proteose from the urine of nephritic patients. The proteose is electrophoretically characterized by its position dominantly at alpha-1 and extending almost to the alpha-2 position, and yielding a strongly positive carbohydrate reaction with a periodic acid Schiff reagent. In cases where an acute glomerulonephritis had apparently recovered, the proteose had disappeared from the urine, but it was present in all of a mixed group of cases of chronic glomerulonephritis. Some degree of proteosuria also accompanied pyelonephritis with obstruction and renal disease associated with diabetes. On the other hand, patients who had ordinary proteinuria associated with congestive heart failure had no proteosuria.

These preliminary studies lead the authors to believe that the occurrence of urinary proteose, in contradistinction to protein, may be correlated with active parenchymal renal inflammatory changes.

(Continued on advertising page 50)

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NEW DRUGS

This section on drug preparations, presented as an aid to prescribers, consists of two parts. The first consists of a monograph on a new product of particular interest, selected and described by a competent expert. The second part is a listing of certain new products.

TRIFLUOPERAZINE

Trifluoperazine (Stelzine). This drug is a phenothiazine derivative, one of the members of the more potent piperazine subgroup. No final statement concerning its place among the neuroleptics is yet possible. Its greater effectiveness at small dosages in certain psychotic reactions is matched with a higher incidence of extrapyramidal symptoms.

Indications.—Although chlorpromazine seems as effective in managing the extremely anxious, the hostile, or the hyperactive patient, study has shown that this drug is particularly suitable in two groups of patients:

(a) The withdrawn and inactive long-term "schizophrenic", where its effect may possibly be related to its extrapyramidal action and the mild akathisia (a distressing side effect if marked) and

(b) The patient with marked persecutory delusions who has not responded to other measures.

Its role in neurotic reactions and in symptoms from personality disorders is not yet clear although many of these patients too have been helped when the drug is used as an adjuvant with other therapeutic measures. The method of administration is important. Most authors now recommend an initial 5 mg. b.i.d. or t.i.d. orally, gradually increasing (rarely to more than 30 mg. daily) over a 2- to 3-week period—with constant alertness for side effects and early control of these.

Side Effects.—Extrapyramidal symptoms are frequent (40% or more) and are of three types: (i) dyskinesia, (ii) akathisia and (iii) Parkinsonism. They lessen as the dosage is decreased and anti-parkinsonian drugs are given. The dyskinetic syndromes are varied and may be alarming. (Tics, tonic or myoclonic contractions, and even oculogyric spasms can occur.) Drowsiness, anorexia and dizziness when present usually clear spontaneously. Hypotensive symptoms, depression and blurred vision are rare. Antihistamines usually control any skin reactions.

Toxicity and Contraindications.—Thus far no serious toxic effects on liver, kidney or blood-forming tissues have been reported. An occasional "trace" of urobilinogen may be found on urinalysis. Yet the existence of liver or kidney disease is usually seen as a contraindication to phenothiazine derivatives.

REFERENCES

1. FREYHAN, F. A.: *Am. J. Psychiat.*, 115: 577, 1959.
2. HIMWICH, H. E.: *Ibid.*, 115: 756, 1959.
3. Trifluoperazine: Clinical and pharmacological aspects, The Macmillan Company, New York, 1959.

This listing of new products is based on information received from Dean F. N. Hughes, Faculty of Pharmacy, University of Toronto, and the *Canadian Pharmaceutical Journal*, to whom we owe thanks.

SEDATIVES, HYPNOTICS, TRANQUILLIZERS AND ANTIEMETICS

217 MEP (Frosst)

Description.—Each tablet contains: Acetophen (acetylsalicylic acid) 200 mg., phenacetin 150 mg., caffeine citrate 30 mg., meprobamate 200 mg.

Indications.—Pain accompanied by muscle spasm and anxiety, as in tension headache, low back pain, menstrual stress, bursitis, rheumatoid arthritis, postoperative pain, etc.

Administration.—One or two tablets 3 times daily.

How supplied.—12 and 100.

282 MEP (N) (Frosst)

Description.—Each tablet contains: Acetophen (acetylsalicylic acid) 200 mg., phenacetin 150 mg., caffeine citrate 30 mg., codeine phosphate 15 mg., meprobamate 200 mg.

Indications.—Pain accompanied by muscle spasm and anxiety, as in tension headache, low back pain, menstrual stress, bursitis, arthritis, postoperative pain, cancer, etc.

Administration.—One or two tablets every 4 to 6 hours as required.

How supplied.—12 and 100.

SINUTAB (Warner-Chilcott)

Description.—Each tablet contains: N-acetyl-p-aminophenol 150 mg., phenacetin 150 mg., phenyltoloxamine dihydrogen citrate 22 mg., phenylpropanolamine HCl 25 mg.

Indications.—Sinus headache.

Administration.—Adults, at first symptoms, 2 tablets followed by one every 4 hours.

Children (6 to 12 years), one-half adult dosage.

How supplied.—30.

Levomepromazine (NOZINAN (Pr), Poulenc)

Description.—Levomepromazine, neuroleptic agent.

Indications.—In psychiatry: Selective action in severe depressive conditions of the melancholic type. Also to control psychomotor agitation and excitement, confusional states, schizophrenia, chronic delirium, anxiety states, phobias and obsessions.

Administration.—Dosage is essentially individual.

How Supplied.—Tablets: 5 mg., 25 mg., 50 mg.; bottles of 50, 500 and 1000 tablets.

Ampoules.—1 ml. (25 mg.) and 2 ml. (5 mg. per ml.); boxes of 10 and 100.

Proclorperazine (STEMETIL 5 mg. Suppositories (Pr), Poulenc)

Description.—Suppositories containing 5 mg. proclorperazine base.

Indications.—Nausea, vomiting and emotional disturbances in younger children.

Administration.—1 or 2 suppositories per day.

How supplied.—10 and 100.

Proclorperazine (STEMETIL 10 ml. vials (Pr.), Poulenc)

Description.—Multidose vials of 10 ml. containing 5 mg. proclorperazine (as methanesulfonate) per ml.

Indications.—Nausea and vomiting of widely varied etiologies; migraine and vertigo; mild and moderate mental and emotional disturbances.

Administration.—Deep intramuscular injection. Generally, the daily dose (per 24 hours) should not exceed 40 mg.

Ergotamine (CAFERGOT-PB (Pr), Sandoz)

Description.—Each coated tablet contains: ergotamine tartrate 1 mg., caffeine 100 mg., bellafoline 0.125 mg., sodium pentobarbital 30 mg.

Indications.—Treatment of migraine: prevents gastrointestinal symptoms and relaxes nervous tension.

Administration.—Two tablets at commencement of attack. If necessary, 1 or 2 tablets every ½ hour thereafter until relief obtained, up to 6 tablets daily.

How supplied.—20, 100, 500.

Meperidine (PHYTADON (N), B.D.H.)

Description.—Pethidine HCl (meperidine HCl), morphine-like analgesic, with mild spasmolytic and sedative-potentiating action.

Indications.—For relief of severe pain, especially of the gastro-intestinal, biliary and genito-urinary tracts; for preanæsthetic medication and for control of postoperative pain.

Contraindications.—Increased intracranial pressure, respiratory depression; marked hepatic dysfunction.
Administration.—Orally or intramuscularly, 50 to 150 mg.
How supplied.—Tablets, 50 mg., bottles of 100 and 1000.
Ampoules, 1 ml. 50 mg. and 1 ml. 100 mg., boxes of 6, 25 and 100.
Vials of 20 ml., 50 mg. per ml. and 100 mg. per ml.

ANTIMICROBIAL AGENTS

PYRIDIUM TRI-SULFA (Pr) (Warner-Chilcott)

Description.—Each tablet contains: Pyridium (phenylazodiamino-pyridine HCl) 150 mg., sulfadiazine 167 mg., sulfamerazine 167 mg., sulfamethazine 167 mg.
Indications.—For analgesic and anti-infective action in urinary tract infections.
Contraindications.—Chronic glomerulonephritis; pyelonephritis of pregnancy with gastro-intestinal disturbance; severe hepatitis where excretion is low; uræmia.
Administration.—Adult dose: one tablet four times daily.
How supplied.—30.

Hexetidine (STERI/SOL, Warner-Chilcott)

Description.—Hexetidine (bis-1, 3-beta-ethyl-hexyl-5 methyl - 5-amino - hexahydropyrimidine) solution, a broad-spectrum bactericide and fungicide for topical application.
Indications.—Bacterial and fungal infections of the mouth and throat.
Administration.—Apply by swab to local lesions; for buccal and pharyngeal lesions, swish in mouth and gargle for 30 seconds, using 15 c.c., morning and night.
How supplied.—7 fl. oz., 14 fl. oz.

Penicillin G (HYLENTA MITIS CD Tablets (Pr), Ayerst)

Description.—Each tablet contains 250,000 I.U. penicillin G potassium in a film-coated, acid-resistant, alkali-soluble base, for controlled disintegration.
Indications.—For prophylaxis, for mild infections, or for pædiatric use in conditions caused by penicillin-sensitive organisms.
Administration.—One tablet three times daily.
How supplied.—12 and 100.

Penicillin G (HYLENTA FORTIS AR Tablets (Pr), Ayerst)

Description.—Each tablet contains 1,000,000 I.U. penicillin G potassium with acid-resistant coating.
Indications.—Where maximum blood levels are desired in treating penicillin-sensitive infections amenable to oral therapy.
Administration.—One tablet twice daily.
How supplied.—12 and 100.

Penicillin V (V-CILLIN K SULFA Tablets (Pr), Lilly)

Description.—Each tablet contains: 'V-Cillin K" (penicillin V potassium, Lilly) equivalent to penicillin V, 125 mg. (200,000 units), sulfadiazine 0.167 g. (2⅝ gr.), sulfamethazine 0.167 g. (2⅝ gr.)
Indications.—Especially in prophylaxis and treatment of mixed infections of the respiratory, gastro-intestinal, and urinary tracts. Organisms susceptible to its action include a wide range of Gram-positive and Gram-negative pathogens, such as streptococci, pneumococci, staphylococci, and *Escherichia coli.*
Administration.—Usual dosage: Adults and older children —1 or 2 tablets four times daily (based on sulfonamide content).
How supplied.—12.

Neomycin, Gramicidin (BIOMYDRIN OPHTHALMIC, Warner-Chilcott)

Description.—Sterile, aqueous, isotonic solution with methylcellulose, buffered at pH 7.0. Contains: neomycin sulfate 0.1%, gramicidin 0.005%, thonzylamine HCl 0.125%, boric acid 1.2%, phenylephrine HCl 0.125%, preserved with thimerosal 0.002%.
Indications.—Ocular infections and ocular allergy especially where allergy and infections coexist.
Administration.—Instil 1 or 2 drops into the eye(s) 3 or 4 times daily.
How supplied.—10 c.c. plastic Dropamatic bottle.

Spiramycine (ROVAMYCINE Suppositories (Pr), Poulenc)

Description.—Each suppository contains 500 mg. spiramycine base.
Indications.—Infections due to sensitive organisms, especially Gram-positive organisms, respiratory-tract infections, whooping cough, acute or chronic otitis media, furunculosis, pyodermatitis, etc.
Administration.—Adults: 2 suppositories, 3 times daily. Children: 1 suppository, 4 times daily. Infants from 6 months to 1 year: 1 suppository 3 times daily.
How supplied.—10 and 100.

Spiramycine (ROVAMYCINE Pædiatric (Pr), Poulenc)

Description.—Bottle of 60 ml. containing 25 g. of dry mixture for oral suspension. The suspension formed by adding 40 ml. distilled water contains 125 mg. spiramycine base per teaspoonful (5 ml.), in a pleasantly flavoured combination.
Indications.—Infections in children: whooping cough, acute and chronic otitis media, and other infections due to sensitive organisms; prophylaxis of secondary infections following influenza, measles, etc.
Administration.—50 to 100 mg. per kg. of body weight (22 to 45 mg. per lb.) per day, depending on severity of the case.
How supplied.—60 ml. bottles containing 25 g. dry mixture.
Rovamycine Oral Suspension is also available in bottles of 115 ml.

MISCELLANEOUS

ANTURAN (Pr), (Geigy)

Description.—Sulfinpyrazone, a potent uricosuric agent chemically derived from phenylbutazone.
Indications.—To reduce blood urate levels and promote absorption of tophi in chronic tophaceous and acute intermittent gout.
How supplied.—Tablets 100 mg., bottles 100 and 1000.

BRAVISOL, (Stiefel)

Description.—Fused synthetic aluminum oxide—a non-silicon abrasive—plus hexachlorophene 1% in an "acne-aid" base of soap and synthetic detergent. Three grades—Fine, Medium and Rough.
Indications.—Provides cleansing action and abrasive effect for long-term superficial abrasion in treatment of acne.
Use.—Follow instructions carefully, using Fine for initial treatment, Medium for second stage and Rough for maintenance.
How supplied.—Fine, 6 oz. jars; Medium, 6½ oz. jars; Rough, 7 oz. jars.

LOFENALAC (Mead Johnson)

Description.—A balanced low phenylalanine food made from a special casein hydrolysate low in phenylalanine combined with fat (corn oil) and carbohydrate (Dextri-Maltose and arrowroot starch).
Vitamins and minerals are included to provide amounts similar to those in the usual milk formulæ.
Indications.—For use as the sole or main source of nourishment for infants and children with phenylketonuria (or phenylpyruvic oligophrenia) which is due to a congenital inability properly to metabolize the essential amino acid phenylalanine.
If the condition is allowed to progress, brain development is arrested, and severe mental deficiency develops.
Administration.—Must be controlled by physician. Should not be fed to normal children.
How supplied.—In powdered form, for mixing with water, 2½ lb. cans.

(To be continued)

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GENERAL PRACTICE

THE LIVER FRICTION RUB*

L. D. WILCOX, M.D., F.R.C.P.[C], *London, Ont.*

ABDOMINAL auscultation still seems to be the neglected child of physical examination in the literature and in practice (Thorek). While a few clinicians have tried to stress its importance, the average doctor does not include it in his diagnostic armamentarium.

In 1938, a 27-year-old woman came into hospital with weakness and a temperature of 104° F. She had had attacks of diarrhœa over a period of six years and prior to admission she lost more than 30 lb. in weight. On examination she was undernourished. The liver was generally enlarged and a round swelling was noted over its anterior surface in the epigastrium. A friction rub was audible over the point of maximal swelling. It was obvious that the condition was critical, and with the story of diarrhœa and fever it seemed likely that the patient had a liver abscess. An aspiration failed to recover pus but the contents of the needle were expelled into formalin and sectioned. To our surprise the diagnosis was carcinoma. This was confirmed at exploratory laparotomy and at autopsy, where it was found that the patient had polyposis involving the entire colon and the duodenum with malignant changes in both these parts in association with secondary deposits in the liver.

The case impressed on me the import of a friction rub over the liver. It reminded me that inflammatory conditions in the liver did not usually produce friction rubs.

There is no such thing as a new physical sign. However, with the appearance of so many diagnostic tests for elucidating the causes of upper abdominal pain it is well to remember that the use of the stethoscope will sometimes clarify a case which has remained unsolved.

I have had several opportunities for observing this sign and I shall record my experience with it.

Allbutt and Rolleston in their textbook written in 1910 stated that in cancer of the liver a rub can be both felt and heard over the liver in some cases. This, they claimed, pointed either to local peritonitis or the presence of a cancerous nodule in the parietal peritoneum against which a cancerous nodule in the liver was rubbing. They pointed out that peri-hepatitis with a friction also occurred sometimes in association with cirrhosis of the liver and they explained the pain which cirrhotic patients experience on this basis.

CASE 2.—A farmer, 50 years of age, was admitted to hospital in December 1953, complaining of very severe right upper quadrant pain. He gave a history of pain in the epigastric area during the previous four months. This pain was not related to food and it had increased to a point where he was forced to stop work 10 days before admission. The pain during this period was aggravated by any body movement. It was so severe that "it took his breath away" and it had required morphine for its control before his admission to hospital.

On physical examination the patient was in great distress. He remained in a fixed position on his back and resisted any movement. The abdomen seemed semi-rigid and it was tender on palpation over its upper half — especially on the right side. Pressure over the enlarged liver produced shoulder-tip pain. There was no evidence of ascites. A friction rub was palpable and audible over the liver. It was suspected that this man had carcinoma of the liver secondary to a large bowel new growth. The barium enema examination was negative, however. It was proposed to do an upper gastro-intestinal series, but the patient was in so much pain that instead of taking him to the radiology department it was decided to carry out a careful liver biopsy. This was done without any difficulty and it revealed a bile duct carcinoma. The patient was sent home on meperidine (Demerol) every four hours. He died shortly after he was discharged from hospital.

CASE 3.—A woman, 49 years of age, had had a carcinoma of the uterus operated on in 1943. She was seen in 1958 on account of fever, with a temperature ranging between 102° and 103° F.

Physical examination showed pallor, slight jaundice, distended veins, and a fever of 103° F. The liver was grossly enlarged and a loud friction rub was heard over its anterior surface. On this single finding it seemed likely that the patient had an extension of her primary disease from the pelvis to the liver. She died two weeks later.

CASE 4.—A man, 74 years of age, was seen in August 1957, because of right upper quadrant pain which was aggravated by deep breathing. He had occasional vomiting. The physical examination showed a smooth enlarged liver which was tender. There was no splenic enlargement. A friction rub was audible over the anterior surface of the liver. The patient had had a previous operation for prostatic carcinoma. He was treated with Largactil (chlorpromazine) and meperidine. The condition gradually worsened. The friction rub remained audible from September 3 to September 18. At postmortem examination the liver weighed 5900 g. It was finely nodular. Its surface was covered with a thin film of organizing exudate with recent adhesions to the diaphragmatic surfaces and to the regional structures. The entire organ was infiltrated with new growth which proved to be an anaplastic carcinoma of the prostate. It had metastasized to lymph nodes, liver, stomach and lungs. Because of the presence of the friction rub in this case, it was felt that it would not be necessary to investigate further.

CASE 5.—In 1946, a chronic alcoholic, 60 years of age, was seen because of pain in the right side of his abdomen. This pain was aggravated by deep breathing. On examination the liver margin was found 12 cm. below the costal margin in the mid-clavicular line. A friction rub was heard over the anterior surface of the enlarged liver. This friction persisted for several days and then disappeared. In the next five years it was never heard again. No ascites developed. The liver gradually decreased in size, and the patient moved from the stage of fatty enlargement caused by alcoholism

*Read at the Annual Meeting of the Canadian Medical Association, Halifax, N.S., June 1958.

to the classical picture of cirrhosis. This is the only example of a friction rub in the course of cirrhosis which I have encountered. It has been described in this condition before ascites develops.

CASE 6.—A 62-year-old man was admitted to the psychiatric service because of mental changes, pain, weight loss, and fever. His examination revealed an indefinite upper abdominal mass. A barium meal showed carcinoma of the antral portion of the stomach. A surgical consultant felt that while the patient looked very ill he might be helped by resection of the stomach. Because I suspected liver enlargement I doubted whether operation would do the patient any real good. Finally, when we were all ready to agree to an exploratory operation, a very marked friction rub developed over the enlarged liver. Because of my previous experience I took the stand that this must surely represent secondary carcinoma of the liver; on this account the patient was allowed to go home, where he died four weeks later. At autopsy the liver weighed 6000 g. and the lesion proved to be a carcinoma secondary to a new growth in the stomach.

SYMPTOMS

Pain in the epigastrium or in the right upper quadrant is characteristic of this condition. It is dull or excruciatingly sharp in character. The pain is aggravated by breathing, coughing or moving. It may last for days or weeks. It is often associated with the feeling of fullness or heaviness in the right side of the abdomen which is increased if the patient turns on his left side. The pain may radiate to the right shoulder. In association with the pain the patient is likely to have many of the symptoms expected with widespread malignancy of the liver.

SIGNS

The friction rub is leathery in character and it is found over an enlarged liver in the epigastrium or the right upper quadrant. It is audible and not infrequently palpable. The friction rub is sometimes noted at the anterior costal margin and has been described as resembling "the crunching of new snow". There is pronounced tenderness and muscular spasm at the site of pain, usually in the right upper abdominal quadrant, indicating an underlying peritoneal irritative process. Very often a nodular anterior surface is noted. Pressure over the liver may give pain in the right shoulder region. It is well to note that the friction rub may come and go, and it may persist for long periods after it has ceased to be associated with pain.

The differential diagnosis must be made from the friction that occurs over an enlarged spleen in the left upper quadrant. There is no difference between these two frictions except that of position. Enlargement of the spleen is unusual in liver carcinoma. It is not infrequent to mistake bowel sounds for liver friction, but one should remember that such sounds are irregular, not leathery in character, and not consistently related to respiration. Rarely, malignancy of the peritoneum without associated ascites may be responsible for a friction rub which is linked with respiration.

If a friction rub is discovered over the liver, does it mean carcinoma or cirrhosis? The latter condition is likely to be associated with a characteristic history of alcoholism, and liver function tests will give evidence of diffuse liver involvement. In many such cases the spleen is enlarged whereas in liver malignancy enlargement of the spleen is unusual.

Liver friction was found in:

Primary bile duct carcinoma		1
Secondary liver carcinoma		10
Stomach	3	
Pancreas	1	
Colon	1	
Uterus	2	
Bronchus	1	
Prostate	1	
Breast	1	
Lymphoblastomas		2
Cirrhosis		2

From this study it will be seen that the presence of a friction rub over the liver in this experience suggests that the patient probably has some malignancy of the liver. This is likely to be a secondary carcinoma but in rare instances it will be primary and, as Dr. Sheila Sherlock* has noted, the sign may be the first indication that a patient has a primary carcinoma of his liver. Dr. Ernest Maltby* has pointed out that the sign may be noted in Hodgkin's disease when this process involves the liver.

Its significance revolves around neoplastic conditions which may or may not be associated with tumour necrosis with extension to the liver capsule in such a way as to stir up a reaction of the overlying parietal peritoneum. As in pleurisy, some liver friction rubs are painless, but most patients with this condition experience very severe pain. It is also worth noting that a friction rub may come and go. Since we have been looking for this sign routinely from day to day in patients with liver carcinoma, we have been surprised to find that a liver friction rub does not always persist. When it disappears, it is probably as a result of the development of ascites. This is well supported by the fact that at postmortem examinations even in patients with friction rubs before death the pathologist rarely notices a collection of fibrinous exudate over the involved area.

The treatment of this condition is the same as the treatment of an acute pleurisy. Mustard plasters for 20 minutes every six hours often give patients very real relief. Failing help from this old-fashioned remedy, the use of meperidine, chlorpromazine, morphine, or T.O.A. may be needed. In cases where the pain is intractable and where it cannot be controlled with any of these measures, the addition of 500 c.c. of 2% Novocain (procaine) in normal saline to the peritoneal cavity or the induction of a pneumoperitoneum will separate the liver from the abdominal wall and give the patient immediate relief.

It is interesting that inflammations of the gallbladder and of the liver do not produce a form of peritoneal reaction which gives rise to a friction. The peritonitis in these pyogenic and acute conditions is probably plastic and it tends to splint the action of the liver and diaphragm, so that move-

*Personal communication.

ment is not as free as it would be in the conditions which have been mentioned. Hepatitis never leads to a liver friction rub. While infarcts of the spleen often give rise to upper abdominal friction rubs, it is well to remember that liver infarcts are never large enough (because of the double blood supply to the liver) to lead to this type of surface reaction.

CONCLUSION

Everyone who deals with liver malignancy or cirrhosis will be rewarded by the help which the stethoscope can bring him if he searches the liver area for this sign every time he visits a patient with these conditions. Its presence allows the doctor to explain the pain to the patient. It makes the management of this particular phase of the patient's illness much more certain and effective.

This single sign of the friction rub may be the only explanatory finding in the patient complaining of upper abdominal pain when the radiographs and all other tests are completely negative. It never occurs in heart failure, amyloidosis, hepatitis, liver abscess, gall-bladder inflammation or miliary liver abscesses seen with cholangitis. It occurs occasionally with cirrhosis of the liver.

719 Waterloo St.,
London, Ont.

Association Notes

MEDICAL CENSUS OF CANADA, MAY 1959

The Department of National Health and Welfare periodically brings up to date its information on the medical population of Canada by means of questionnaire surveys. A survey in this series is being conducted in May of this year.

At the time of the last survey by the Department, in June of 1954, civilian doctors in active practice numbered 15,651. We have reason to believe that the total now approximates 19,000. Aspects of this increased supply, such as geographic distribution, the effects of medical immigration, and distribution by age, sex, specialty and type of work, will all be studied from the new survey data. In addition, the survey will provide information which will usefully supplement the C.M.A. survey of salaried physicians.

You will be receiving, through the mail, a questionnaire, and you are urged to complete it and return it promptly to the Research and Statistics Division of the Department of National Health and Welfare, Ottawa. In the event that your mail copy does not reach you, the questionnaire will be reproduced in the May 15th issue of the Journal for your convenience.

This survey has the full support of the Canadian Medical Association. It now remains for all of us to stand up and be counted.

RECENSEMENT MEDICAL AU CANADA EN MAI 1959

Périodiquement, le ministère de la Santé nationale et du Bien-être social met à jour, au moyen de questionnaires, ses renseignements sur le nombre des médecins au Canada. Un relevé de ce genre se tiendra pendant le mois de mai de la présente année.

A l'époque du dernier relevé effectué par le Ministère au mois de juin 1954, le nombre des médecins civils qui exerçaient s'élevait à 15,651. Nous avons raison de croire que ce nombre est parvenu, à l'heure actuelle, à près de 19,000. Les aspects qui se rapportent à cette augmentation, comme la répartition géographique, les effets de l'immigration de médecins, ainsi que la répartition par âge, sexe, spécialité et genre de travail, seront étudiés à l'aide des données que le nouveau relevé fournira. En outre, ce relevé donnera des renseignements qui viendront s'ajouter utilement au relevé des médecins salariés, effectué par l'Association médicale canadienne.

Vous allez recevoir par la poste un questionnaire que vous êtes prié de remplir et d'expédier promptement à la Division de la recherche et de la statistique, du ministère de la Santé nationale et du Bien-être social, à Ottawa. Au cas où vous ne recevriez pas par la poste un exemplaire du questionnaire, celui-ci sera publié pour votre commodité, dans le Journal, livraison du 15 mai.

L'Association médicale canadienne accorde son entier appui au présent relevé. Il nous appartient tous maintenant, de répondre à l'appel.

HOSPITALS AND INTERNS

A. D. KELLY, M.B.

The Canadian Intern Placement Service, an important activity of C.A.M.S.I., has concluded its task for the current year in assigning the members of the classes of 1959 at the nine participating medical schools to the C.M.A.-approved hospitals of their choice. A total of 407 Canadian students utilized the Service and 365 (89.7%) were assigned to the hospital of their first choice, 29 (7%) to the hospital of their second choice, and 12 (2.8%) to their third choice or lower; none was unplaced. This is not surprising in view of the fact that the number of approved internships considerably exceeds the number of available Canadian graduates. C.I.P.S. operates on our cherished principle of freedom of choice, and senior students commonly investigate the merits of several hospitals and file multiple applications to be sure of selection by a hospital high in their preference. The moment of truth arrives when students and hospitals are obliged to list in their order of preference the hospitals and the students which each actually desires. The outcome is sometimes disappointing to hospitals which have gathered impressions that they stand high in the regard of applicants whereas they may be classified by the students as second choice or lower.

A not uncommon reaction of administrators and intern committees is to blame C.I.P.S. for their failure to fill their quota, despite the fact that they know that the Service does not and cannot influence the choice of either students or hospitals. A refreshing change is the attitude adopted by the Medical Superintendent of the Hamilton General Hospital, who has addressed the following letter to applicants desired

by the hospital but who have chosen another and have been assigned elsewhere by C.I.P.S.

"Dear Mr. —:

"You have applied to this hospital for a junior rotating internship. We have received our allotment from C.I.P.S. and noted that you were not among those interns assigned to us. This is undoubtedly because you have indicated a greater preference to intern in some other hospital and have been placed in that hospital by C.I.P.S. and been accepted. I sincerely hope that your internship is a good one and that you are happy in the hospital of your choice. We are naturally disappointed that you were not assigned to us by your own preference, but in no way wish to criticize your action since your choice of hospital must, in the final analysis, be a personal decision.

"We do wish, however, to ask you to assist us in one matter. We are attempting always to improve upon the internship offered by this hospital. We can be helped to do this by you. I would be extremely interested in knowing to which hospital you have been assigned, and in knowing the reasons for your preference of the internship offered in this hospital to our own.

"We feel we can, knowing your reasons for preference, improve upon our own situation and in so doing comply with the desires of C.A.M.S.I. to do this very thing. A copy of this letter has been sent to C.A.M.S.I. so that that organization might see here an honest attempt to improve our local conditions of internship.

"A stamped, self-addressed envelope is enclosed to facilitate your reply.

"I hope to hear from you. Again good luck in the coming exams and the coming year.

Sincerely,
(Signed) JOHN M. PHIN, M.D.,
Medical Superintendent"

Dr. Phin reports that the response has been gratifying and that long, interesting letters have been received from over half of his applicants who decided to go elsewhere. Two factors predominate: (a) a decision to take the basic rotating internship in a university hospital to facilitate subsequent specialty training, and (b) the effect of marriage and family responsibilities which make it difficult to uproot the wife and children, give up the flat and proceed to a new location which provides an otherwise desirable internship.

This effort at self-appraisal is commendable. Already the practical proposal to provide married quarters has emerged, and doubtless further suggestions for improvement to make the internship more attractive will be forthcoming.

DR. RENAUD LEMIEUX

At the 35th Council Session of The World Medical Association held in Sydney, Australia, March 25 to April 5, Dr. Renaud Lemieux of Quebec City, Past-President of The Canadian Medical Association, was elected to fill the vacancy as President-Elect of the W.M.A. for the term 1958-1959. It is expected that this election will be confirmed by the delegates of the XIII General Assembly of The World Medical Association in Montreal, Canada, next September, whereupon Dr. Lemieux will be installed as twelfth President of that Association.

MEDICAL MEETINGS

15TH BRITISH CONGRESS OF OBSTETRICS AND GYNÆCOLOGY

The Fifteenth British Congress of Obstetrics and Gynæcology will be held in Cardiff on July 14, 15 and 16, immediately preceding the C.M.A.-B.M.A. meeting in Edinburgh. Applications for membership are still being received. Those desirous of attending the Congress are advised to apply without delay to the Honorary Secretaries, 15th British Congress of Obstetrics and Gynæcology, The Maternity Hospital, Glossop Terrace, Cardiff, Wales, from whom all particulars may be obtained.

FRACTURE COURSE, NIAGARA FALLS

The provisional program for the fracture course organized by the Niagara Falls Medical Society for October 7, 8 and 9, and conducted by Dr. Preston A. Wade and Sir Reginald Watson-Jones, is as follows:

First Day: Manipulative treatment of fractures (R.W.-J.); Operative treatment of fractures (P.A.W.); Joint stiffness after injury (R.W.-J.); Value of joint motion in the treatment of fractures (P.A.W.).

Second Day: Fracture-dislocations of the ankle: manipulative (R.W.-J.) and operative (P.A.W.); Supracondylar fractures of the femur in the elderly (P.A.W.); Fractures of the upper shaft of the femur (R.W.-J.); Injuries of the wrist joint (P.A.W.); Injuries of the elbow joint (R.W.-J.).

Third Day: Minor joint injuries (R.W.-J.); Multiple and autocrash injuries (P.A.W.); Treatment of ununited fractures (R.W.-J.); General discussion or other special topics (P.A.W. and R.W.-J.).

Information from Dr. R. G. Warminton, Niagara Falls Medical Society, Niagara River Parkway, Chippawa, Ont.

CANADIAN ASSOCIATION OF PHYSICAL MEDICINE AND REHABILITATION

The Canadian Association of Physical Medicine and Rehabilitation will hold their Seventh Annual Meeting in the Lord Nelson Hotel, Halifax, N.S., June 4-6, 1959. Physicians who are interested in physical medicine and rehabilitation are most welcome to attend this conference. All enquiries or requests for information about the presentation of papers should be addressed to the Secretary, Dr. M. Mongeau, 6265 Hudson Road, Montreal 26, Que.

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CANADIAN RHEUMATISM ASSOCIATION — SOCIETE CANADIENNE DE RHUMATOLOGIE

The annual business meetings of the Canadian Rheumatism Association (Société Canadienne de Rhumatologie) will be held during the Pan American Congress on Rheumatic Diseases in Washington, D.C., June 2-6, 1959. Members are also invited to attend a special Heberden Society meeting at Buxton, England, on July 25, 1959. The Secretary of the Canadian Rheumatism Association is Dr. de Guise Vaillancourt, Hôtel-Dieu Hospital, Montreal 18, Que.

CANADIAN OTOLARYNGOLOGICAL SOCIETY – SOCIETE CANADIENNE D'OTOLARYNGOLOGIE

The Annual Meeting of the Canadian Otolaryngological Society (Société Canadienne d'Otolaryngologie) will be held at the Sheraton-Brock Hotel, Niagara Falls, Ontario, October 9 and 10, 1959, under the presidency of Dr. G. Arnold Henry, Toronto. The Secretary of the Society is Dr. Donald M. MacRae, 324 Spring Garden Road, Halifax, N.S.

LETTER TO THE EDITOR

SULFAMETHOXYPYRIDAZINE (KYNEX)

To the Editor:

Because of enquiries received, following the reporting by Blanchard and Mertens in the *Canadian Medical Association Journal* (79: 627, 1958) of three cases of interstitial myocarditis, suggested to have been caused by the use of sulfamethoxypyridazine (Kynex), a thorough study of experience with this drug by eminent investigators throughout the world has been obtained, with the following summarized results.

Investigation conducted on a large series of autopsies has shown that up to 44.5% of people who have had sulfonamide therapy within 30 days of death will show interstitial myocarditis, regardless of the cause of death. The fact that autopsy specimens on patients who received sulfonamides more than 30 days before death demonstrate no signs of myocarditis, points up the finding that this myocarditis is a reversible condition.

It has also been pointed out by various authors that it may be the cause of death in patients in whom a marked hypersensitivity has been developed. Therefore, it would be reasonable to say that if death intervenes for whatever cause during the course of sulfonamide therapy, it would be expected that a significant percentage of these patients would have microscopic lesions of the type classified as interstitial myocarditis. It does not follow, however, that the presence of this condition is pathognomonic of its being the cause of death, as the great majority are reversible. Interstitial myocarditis, as a hypersensitivity reaction to drugs and more particularly sulfonamides, is a phenomenon that has been noted in medical literature for over 15 years. Authorities when speaking of interstitial myocarditis have routinely referred to it as a hypersensitivity reaction in contradistinction to a toxic reaction of the drug.

Thus, the development of interstitial myocarditis appears to be the result of a flaw in the patient's own immunological make-up. The list of agents and diseases said to produce this hypersensitivity reaction is great. It includes bacterial endocarditis, coronary thrombosis, syphilis, leukæmia, trichinosis, anaphylactic serum sickness, iodine, streptomycin, penicillin, diphtheria injection, scarlet fever, sulfonamides, carcinoma, and many others. It is evident that this is not a phenomenon related to any specific compound or condition.

It is also of interest to note the following recorded information:

1. No cases of interstitial myocarditis, other than those of Blanchard and Mertens, have been reported to have occurred during or after sulfamethoxypyridazine (Kynex) therapy. This includes not only the United States and Canada, but also all overseas areas.

2. For outside opinion, we contacted, for example, Dr. Rune Frisk, a world authority on sulfonamides and one of the original clinical investigators studying Kynex. He stated that no such similar case has been seen in Sweden, where large amounts of Kynex are used, and he believes that this experience with Kynex in Canada is unique.

3. Side effects from Kynex given in the recommended manner are similar in type to those reported for the other sulfonamides and are less frequent in incidence.

4. An analysis of prescriptions written for Kynex in the U.S. only, *not* including Canada or overseas, in the past year reveals that over two million have been filled. This means an incidence of three per two million for interstitial myocarditis reported, an extremely low rate of reaction by any standard.

5. In spite of the lower incidence of reactions with Kynex, we state in the Kynex package circular that any of the reactions described for previous sulfonamides should be looked for with this newer drug. Kynex, being a sulfonamide, may thus have reactions similar to other sulfonamides. The Council on Drugs of the A.M.A. states: "Except for a diminished incidence of renal toxicity, the same general type of side effects and untoward reactions may be expected with sulfamethoxypyridazine as with other sulfonamides. Hence, the drug should be used with the same precautions and is subject to the same contraindications as other agents of this class. (See the general statement on sulfonamides in *New and Non-official Drugs.*)"

Thus, in summary, we feel, as Dr. Frisk does, that the experience reported at Sunnybrook is unique, and if Kynex is condemned by some practitioners, we feel this is unjust. The recent report by Dr. Welch of the FDA reports that in the year 1956, 301 cases of anaphylactoid reactions occurred after the use of penicillin. This is mentioned to point out that any potent antibacterial does carry with it some unusual element of risk because of hypersensitivity reactions of patients. The difference is that we are not surprised when it occurs with penicillin, even though it is seen more often. Many are surprised when hypersensitivity reactions occur with sulfonamides and therefore feel that it is the drug that is at fault. Again, the patient who suffers a hypersensitivity reaction, brings into this

condition an abnormal immunological response in no way related to the true toxicity of the drug.

R. G. WARMINTON, M.D.,
Medical Director.

Cyanamid of Canada Limited,
P.O. Box 330,
Niagara Falls, Ont.,
March 30, 1959.

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THE LONDON LETTER

(From our own correspondent)

NEW HOME FOR THE PHYSICIANS

Ever since the end of the war the question of a new home for the Royal College of Physicians of London has been a topic of recurring interest. A final decision, however, has at last been made, whereby the college will surrender the lease of its site and building on the corner of Pall Mall East and Trafalgar Square in favour of the Government of Canada. The building is to become part of the present Canada House. At the same time the Crown Commissioners will grant the college a lease of the site of Someries House in the south-east corner of Regent's Park, where a new college will be built. It is hoped that work on the building will be started in 1961. It was in 1820 that the college acquired its present site at Pall Mall East, and the building, designed by Sir Robert Smirke, was opened on June 25, 1825. In moving to Regent's Park the physicians are following the example of the obstetricians and gynæcologists, whose new home is on the opposite side of the Park. They are also killing once and for all the possibility, which was revived after the end of the last war, of establishing an Academy of Medicine in Lincoln's Inn Fields.

BIGGER HOME FOR THE SURGEONS

The physicians are being much more modest in their aims than the surgeons. Almost simultaneously with the announcement of the projected move of the physicians, the Royal College of Surgeons of England launched an appeal for £3 million to support its teaching and research program and to cover the cost of its building projects in Lincoln's Inn Fields. The college, which has departments of anatomy, physiology, pathology, pharmacology, anæsthetics, ophthalmology, and dental science, requires a sum of £350,000 a year for its research and teaching activities. In addition, it requires £350,000 for the completion of new buildings at present in progress. As it receives no research grant from the Government, it is entirely dependent upon the generosity of the public for funds to maintain its ambitious program, and this is the first widespread appeal for funds that it has made.

NEW PENICILLIN DEVELOPMENT

Fate seems to have decreed that penicillin should remain a predominantly British contribution to medicine. At least, such is the first reaction to the announcement that what the *Lancet* has described as a "new break-through" has been achieved by a team of research workers in the Beecham Research Laboratories. What these workers have done has been to devise a method whereby 6-amino-penicillanic acid, the basic radicle of penicillin, can be isolated in quantity from the ordinary penicillin fermentation process. What this means, of course, is that the cumbersome method of biosynthesis can now be replaced by straightforward chemical synthesis, starting with 6-amino-penicillanic acid. The long-term effects of this discovery upon the whole field of antibiotics is potentially unlimited, as it may mean that penicillins can be produced against that wide range of organisms that have hitherto been covered only by the so-called "broad-spectrum" antibiotics. The short-term prospects, which are more predictable, are that it should be possible to produce penicillins which can be given to patients who are allergic to the penicillins at present in use. Indeed, there is already preliminary evidence that this is being achieved. It has been said that this is the greatest advance in the penicillin field since Sir Howard Florey and his colleagues at Oxford opened the way to the large-scale production of penicillin in the early days of the last war.

EPSTEIN AND THE DOCTORS

Sir Jacob Epstein would appear to be making a special study of the medical profession at the moment. At least, within a fortnight two bronze busts from his hands have been unveiled—one of Sir Russell Brain, the former President of the Royal College of Physicians of London, and the other of Sir Wilfrid le Gros Clark, Dr. Lee's Professor of Anatomy in the University of Oxford. The unveiling of the latter bust was part of the celebrations marking Sir Wilfrid le Gros Clark's silver jubilee as Professor of Anatomy in Oxford and the opening of the new extensions to his department which have just been completed at a cost of £160,000. Sir Jacob and Lady Epstein were present at both ceremonies. The outstanding feature of the extensions is the new dissecting-room which, according to the *Lancet* "with its 40 ft. double-lensed glass roof, vaulted and heat-resisting, framed with continuous strip-lighting and set into a lemon yellow ceiling, is memorable."

London, April 1959. WILLIAM A. R. THOMSON

THE THIRD PARTY

"In the quest for better health and peace of mind for our people no one denies the need medicine has for Third Party help. However, few recognize or admit the urgent need Third Parties have for help and leadership from medicine. Medicine is not critical of the existence of Third Parties. It is only when these agencies or organizations go beyond their prerogative and destroy treasured ideals of doctor-patient relationships that medicine fights to protect this relationship which answers the inner man's need for security, confidence and trust that bring him peace of mind."—Editorial, *South. M. J.*, 49: 1958.

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OBITUARIES

DR. FREDERICK T. GREEN, 80, died on March 15 after a lengthy illness. Born in Anacapri, Italy, he graduated from the University of Naples in 1906 and did postgraduate work in Britain, the United States, France and Germany. From 1915 to 1920, he was with the R.A.M.C. in France and Italy. A well-known physician in Montreal, Dr. Green served for nearly 30 years on the staff of the Montreal General Hospital, and was actively interested in research work on hæmatology.

He is survived by his widow, two daughters and a son.

DR. C. H. MacNEILL, 56, died at his home in Toronto on March 11 after a long illness. A native of Petitcodiac, N.B., he started to practice medicine in Campbellford, N.B., after graduating from Queen's University in 1929. At the outbreak of World War II he joined the army and served overseas with the rank of major. After the war, as a specialist in pulmonary diseases, Dr. MacNeill was on the staff of the Peterborough Military Hospital and then moved to Kingston Military Hospital. In 1947 he transferred to the Christie Street Hospital, Toronto, and then to Sunnybrook Hospital, where he served on the Canadian Pension Commission.

Dr. MacNeill is survived by his widow.

DR. WILLIAM PEARSON died in Toronto on March 11. He was born in Norfolk County, Ont., and received his medical education at the University of Toronto, where he graduated in 1905. In 1910 he started a practice in Brantford, moving to the Weston area of Toronto in the 1920's. Dr. Pearson was the school doctor in York Township until his retirement four years ago.

He is survived by his widow.

DR. CARL SMITH, 61, died in the Kitchener-Waterloo Hospital, Ont., on March 29, after a brief illness. Born in Paris, Ont., he went to Queen's University, Kingston, and graduated in 1930. He practised for two years in Uxbridge before going to Kitchener in 1933. A specialist in anæsthesia, Dr. Smith was on the staff of the Kitchener-Waterloo and St. Mary's Hospitals.

He is survived by his widow and a daughter.

DR. CHARLES A. STEWART, 84, died on March 15 in the Cornwall General Hospital, Cornwall, Ont. He fractured a hip when he fell on an icy street early in March, and this, together with a heart complaint, resulted in his death. Dr. Stewart was born in Dunvegan, Ont. In 1901, after graduating from McGill University, he started to practise in Moose Creek and Dunvegan, moving to Cornwall in 1923. In 1926 he was appointed Coroner for Stormont County.

Dr. Stewart is survived by his widow, three sons and a daughter.

PROVINCIAL NEWS

BRITISH COLUMBIA

Reports on poliomyelitis in British Columbia for 1958 show that there were 13 cases in the province as against 225 in 1955, when Salk vaccine came into use. There were three deaths, two in the Okanagan and one in the Kootenays. None of these persons had been given Salk vaccine. In Vancouver there were three cases, with no deaths; none had been vaccinated. Vaccination is, on the whole, widely used, over half a million having received it through public health schemes, and many thousands privately. The degree of acceptance in British Columbia is the highest in Canada.

In the constant struggle which exists between hospitals forced to supply up-to-date service along modern lines and a government whose only consideration, or so one often thinks, is to "hold the line" in the matter of costs, tensions tend to mount.

Such is the case in Prince Rupert, where the directors of the General Hospital have resigned. They give two main reasons, we understand. The British Columbia Hospital Insurance Service, under the rule of the Hon. Eric Martin, Minister of Health and Welfare, has turned down the request of the directors for financial help to meet new wage increases. They resent what they call his "arrogant attitude" in this matter. Secondly, they object strongly, and in this they are supported by the British Columbia Hospital Association, to a letter that Mr. Martin wrote to the *Prince Rupert Daily News,* suggesting that "the people of Prince Rupert should press the hospital board for explanation . . . as to why it should go so deeply into deficit."

In the press of March 9, we read that the "nurses' strike has been averted" and we are all very glad that this is so. The strike had been set to take effect on March 12, and eight hospitals on the lower mainland were affected.

The main facts are these. In January, a conciliation board unanimously agreed that graduate nurses in hospitals should have a $20 monthly raise in pay. The hospitals' budgets, as accepted by the British Columbia Hospital Insurance Service, would not meet this—and the B.C.H.I.S., under the control of the Provincial Board of Health and Welfare, would not at first authorize any increase.

The nurses threatened strike action, and finally the Hon. Eric Martin, Minister of Health and Welfare, agreed to the raise, to tak effect April 1. The nurses refused this, as they felt the increase should be retroactive to January 1, and arranged for a strike to enforce their demands. It was really only to be a partial strike but would have affected the hospitals strongly, in the matter of elective operations, etc.

The strike was set for March 12, and there is no doubt that the nurses meant business, and indeed we cannot blame them. But Mr. Martin finally acceded to their demands and gave authority to the hospitals to pay the increase, retroactive to January 1.

An important Occupational Health Conference was held in Vancouver on March 6, organized by the Vancouver Board of Trade and the Greater Vancouver Health League. It was followed on March 7 by a joint

meeting of the Northwest Association of Occupational Medicine and the occupational health nurses of the Registered Nurses' Association of British Columbia.

There were many eminent speakers from the U.S.A. as well as from Canada. Dr. R. H. Lowry of Seattle, of the Space Medicine Branch of the Boeing Airplane Company, spoke on "Conserving human resources". Dr. Eugene Owen, Portland, Past President of the Northwest Association of Occupational Medicine, spoke on "Occupational health in a changing world". Dr. J. F. Tysoe of Victoria was speaker on a panel representing labour, management and medicine. Miss Mildred L. Walker, Ottawa, Senior Nursing Consultant, Occupational Health Division of the Department of National Health and Welfare, spoke on "A partnership—health and work". Dr. J. S. Tyhurst, Head of the University of British Columbia's Department of Psychiatry, spoke on "Mental health in industry".

British Columbia Hospital Insurance will some day cover outpatient and diagnostic services. An amendment to the Hospital Insurance Act has gone through the Legislature, but will not become effective immediately or till the federal plans in this direction are made effective. An Order-in-Council will make this amendment effective, at the will of the Cabinet.

Twenty-eight British Columbia hospitals have received accreditation from the Accreditation of Hospitals Commission of the Canadian Medical Association.

The list includes, besides the major hospitals of Vancouver, Victoria and New Westminster, a large number of smaller hospitals and mental and naval hospitals.

Dr. W. H. Hatfield, President of the Board of Directors of the Vancouver Preventorium, states that the cost of keeping a child at this institution has gone up from $6.37 to $7.64 a day. The Preventorium now cares for 42 children, half of them sufferers from tuberculosis. It will be enlarged to accommodate 70 children.

The Annual Report of the North Okanagan Health Unit was given late in February. It told of the new Health Centre at Salmon Arm and the Vernon Centennial Health Centre recently built; of the home nursing service in Vernon and Coldstream; of improvements in the plumbing code, resulting in better sewage disposal; and a new water system at Lumby.

There was a good deal of epidemic distribution of such diseases as measles, influenza, and infectious hepatitis in one district. A case of suspected rabies in a teen-age child at Okanagan Landing was the result of a bite from an infected bat. The child was treated successfully.

Dr. Stewart Murray, senior medical health officer of the Metropolitan Health Area, reporting on tuberculosis, stated that deaths from tuberculosis in British Columbia have dropped by more than 90% since 1947. In that year there were 536 deaths in a population of 1,044,000 in British Columbia (51.3 per 100,000). Last year, with a considerably larger population (50%), there were 71 deaths (4.6 per 100,000). New cases, however, are constantly being uncovered, especially in the downtown areas of Vancouver, where the rate is 803 per 100,000. The overall average for Vancouver is 106 per 100,000. Taking the province as a whole, it is 4.6 per 100,000.

Home treatment, where possible, is on the increase, with improvement in family and social relations.

Dr. Gordon F. Dowe, assistant professor of pharmacology at the University of British Columbia, has been awarded an $8000 National Heart Foundation grant for studies in electrocardiography.

Dr. John F. McCreary has been appointed Dean of the Faculty of Medicine at the University of British Columbia, succeeding Dr. John Patterson. Dr. McCreary is a graduate of Toronto and came to British Columbia from Toronto, where he was very active in pædiatric work. Here he has been associated with the Children's Health Centre, and with the Medical School of the University of British Columbia where he is professor of pædiatrics.

At the Annual Meeting of the British Columbia Chapter of the College of General Practice of Canada, held at Harrison Hot Springs on March 19-21, Dr. R. A. Stanley of Vancouver was elected President of the Chapter, succeeding Dr. John Granby of Chilliwack. Dr. Stanley has been intimately associated with this work for years.

Others elected to the Executive were Dr. Vincent E. Smith, Victoria, secretary; Dr. A. W. Wallace, Vancouver, treasurer; and Dr. J. B. Anderson, Victoria, Dr. L. S. Chipperfield, New Westminster, Dr. G. A. Gibson, Chilliwaok and Dr. R. A. White, Oliver.

J. H. MACDERMOT

ALBERTA

The Junior Red Cross Crippled Children's Hospital in Calgary has come under new administration and has become the Alberta Crippled Children's Hospital. The original hospital was opened in 1922 in a converted house and served until 1952 when the new hospital with a capacity of 156 beds was put in service. In 1956, the national policy of the Red Cross in relation to the operation of hospitals in built-up areas resulted in release of this institution. After unproductive representations to the provincial government and the City of Calgary, a group of interested citizens in late 1957 organized under the Societies Act as the Alberta Crippled Children's Hospital. In 1958, the hospital was approved as a unit under the new Alberta Provincial Hospital Plan, but continued to operate strictly as an orthopædic hospital, receiving patients from all parts of Alberta. However, in view of the marked decrease in orthopædic cases among children the hospital was placed on an open staff basis effective January 1, 1959, and admission of all children up to 16 was approved.

Notes on Economics

Medical Services (Alberta) Incorporated will no longer pay the accounts of doctors who are not signed-up professional members of the organization. Patients of these doctors who hold a contract with M.S.I. must obtain a receipt from the doctor and submit this to the corporation which in turn reimburses the patient in the amount the contract calls for.

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The Council of the College of Physicians and Surgeons has negotiated a new agreement with the provincial government in respect of the Pensioners' Medical Fund, whereby the grant has been increased from $19 to $24 per eligible person per annum. In the case of an accident where there is third-party responsibility, the doctor is also permitted to claim his account from the third party.

All pensioners who pass the means test become eligible for treatment under the Pensioners' Medical Fund. Since the amount of the grant is based on the cost of care for all ages, the payment to doctors for this special group has amounted to between 50 and 60% of the account presented. The administrators of the fund have been directed by Council to check closely for abuses by both recipients and the profession, with the hope of increasing this percentage.

The Council of the College and the Board of Directors of the C.M.A., Alberta Division, have both come out against the carrying out of elective surgery by surgeons not residents in the hospital area. On the occasions when it is necessary, the physician concerned must ensure that adequate facilities are available and the surgeon is properly qualified.

Under the Hospitalization Benefits Act, the pharmacy committees of the larger hospitals and the Joint Committee of the Associated Hospitals of Alberta and the College of Physicians and Surgeons have been empowered to exert control over drug costs and drug usage in hospitals. In order to help control excessive usage, the Joint Committee last year sent out a list of recommendations regarding the control of drugs within the hospital and is now engaged in a study of comparative costs in 1957 and 1958, which may indicate the efficiency of this move.

A joint committee has been formed with the Alberta Association of Registered Nurses to consider matters of mutual interest between the two professions. Of particular concern at this time are certain intravenous procedures and the removal of sutures, clips and drains which are the physician's responsibility, though they may be carried out under the doctor's supervision if the nurse has had special training. W. B. PARSONS

MANITOBA

Shorter and more effective treatment in sanatoria has made possible a change in hospitals under the Manitoba Sanatorium Board. The King Edward Hospital in Winnipeg is now used for the treatment of chronic and elderly patients. Dynevor Sanatorium has been closed. Sixty beds in Assiniboine hospital, formerly Brandon Sanatorium, and 58 beds in Clear Water Lake Hospital, The Pas, have been set aside for extended treatment patients.

The Manitoba Government has given first reading to a bill which will enable blood transfusions to be given promptly to children despite objections of parents if, in the opinion of the attending surgeon, blood replacement is urgently indicated. The bill was introduced because of the death a few months ago of a boy following a gunshot wound of the thigh. His parents, who were Jehovah's Witnesses, refused to give permission for blood transfusion.

Dr. T. Nicolaides has been recently appointed to the medical staff of Manitoba Sanatorium. He is a graduate of the Medical School of Athens University. Prior to his appointment he spent two years in postgraduate training in New York and for the past year was an intern at the Grey Nuns' Hospital, Regina.
ROSS MITCHELL

A two-day course for physicians and public health workers was held on March 25 and 26 under the sponsorship of the Departments of Pædiatrics and Obstetrics, Faculty of Medicine, University of Manitoba. All the papers and discussions were based on the general topic of problems of the mother and baby at term. Visiting speakers were Professor Helen Wallace, Professor of Maternal and Child Health, University of Minnesota, and Dr. Jean Webb, Chief, Division of Maternal and Child Health, Department of National Health and Welfare, Canada. A total of approximately 150 physicians and graduate nurses attended the sessions. HARRY MEDOVY

NOVA SCOTIA

The Atlantic Regional Meeting of the Royal College of Physicians and Surgeons of Canada will be held in Halifax, Nova Scotia, on Friday and Saturday, October 30 and 31, 1959, which are the last two days of the week of the Dalhousie University Refresher Course. This will be the first of such regional meetings sponsored by the Royal College in its program to provide additional educational opportunities to members of the medical profession engaged in specialist practice.

A cordial invitation is extended to Fellows and certificated specialists of the Royal College of Physicians and Surgeons of Canada living in the Atlantic Provinces and Eastern Quebec to attend this meeting. There will be no fee for Fellows of the College; a registration fee of $10 will be charged to all others attending the meeting.

The meeting will be divided into sections, one for medicine and the medical specialties, and one for surgery and the surgical specialties including obstetrics and gynæcology. The meetings will be held at Dalhousie University and its affiliated teaching hospitals. The program will include presentations by a number of highly qualified guest speakers.

The Chairman of the Program Committee is Dr. R. C. Dickson, Suite 206, Out-patient Department, Victoria General Hospital, Halifax.

Dr. J. M. Corston, Halifax, has been elected a Fellow of the Royal College of Obstetrics and Gynæcology of London. A graduate of Edinburgh University, Dr. Corston served overseas during World War II in the Royal Canadian Army Medical Corps, and has been a member of the Department of Obstetrics and Gynæcology, Dalhousie University, and Victoria General Hospital for the past nine years.

Dr. John Edmond Bethune of Berwick, B.A., D.Sc. Acadia, a 1952 graduate of Dalhousie, has been appointed to the Department of Medicine as an endocrinologist. Dr. Bethune has studied in the past six years in Boston and the Royal Victoria Hospital, Montreal. During the past year he has been in England as a McLaughlin Fellow. In 1957, he obtained his F.R.C.S. (Medicine) Canada.

Three Dalhousie University medical research workers have been awarded National Heart Foundation Fellowships. They are Dr. Don P. MacLeod, M.A., for his work in the study of fundamental causes of abnormal heart rhythms with reference to the importance of body salts, and Drs. S. J. Shane and D. S. Beansland (joint award) for making "comparisons by various methods of the volume of blood flow from healthy and diseased hearts."

Dr. Hereford C. Still was elected President of the St. George's Society of Halifax at the 173rd meeting of the organization held recently in the city.

Dr. A. W. Ormiston presented his resignation as physician to the County of Cape Breton Hospital on February 23. Dr. Ormiston was recently appointed medical examiner for the Dominion Steelworkers Mutual Benefit Society.

Dr. Edward Alexander Nugent, who graduated from the University of Toronto Medical School in 1952, has been appointed assistant professor of surgery, Dalhousie Medical School, and attending surgeon, Victoria General Hospital. This is a full-time appointment. Dr. Nugent undertook postgraduate training in physiology under Dr. A. M. Rappaport from 1953 to 1954. From 1954 to 1956 he was on the Toronto General Hospital rotating services. He spent six months in orthopædic surgery at St. Joseph's Hospital, Toronto, in 1957, and from 1957 to 1958 he studied thoracic surgery at Frenchay Hospital, Bristol, England. He obtained his F.R.C.S. (Canada) in the fall of 1958.

Dr. N. H. Gosse of Halifax was honoured for his work in cancer control at the annual meeting of the Nova Scotia Division, Canadian Cancer Society. A presentation of scrolls was made by Dr. J. P. McGuigan, the Society president. Dr. Gosse has resigned from the Provincial Board but is still a member of the Dominion Board of the Canadian Cancer Society.

At this meeting, Dr. J. G. Kaplan, assistant professor of physiology at Dalhousie University, gave a paper on "Two thousand years of the cancer problem".

The first Cecil E. Kinley lecture was given by Dr. A. J. Rhodes, Director, School of Hygiene, University of Toronto, on "Polio—past, present and future", on Monday, March 16, at the Victoria General Hospital. This lectureship has been endowed by the Nova Scotia Chapter of the Canadian Foundation for Poliomyelitis and Rehabilitation in honour of Dr. Cecil E. Kinley, who is one of the charter members of the Nova Scotia Chapter and has been a leader in the campaign for the control of polio. WALTER K. HOUSE

DIVISIONAL ANNUAL MEETINGS OF THE CANADIAN MEDICAL ASSOCIATION, 1959

Quebec	May 7-9	Chicoutimi
Newfoundland	May 21-23	St. John's
Ontario	May 25-29	Toronto
Nova Scotia	June 23-27	Keltic Lodge, C.B.
P.E.I.	Aug. 28-29	Charlottetown
New Brunswick	Sept. 2-5	St. Andrews
Alberta	Sept. 28-Oct. 1	Edmonton
Manitoba	Oct. 5-9	Winnipeg
British Columbia	Oct. 13-16	Victoria
Saskatchewan	Oct. 19-22	Saskatoon

ABSTRACTS *from current literature*

MEDICINE

Mumps Myocarditis.

G. E. HORTON: *Ann. Int. Med.*, 49: 1228, 1958.

A probable case of mumps myocarditis is presented and the pertinent clinical and laboratory findings are discussed. The possibility of acute coronary insufficiency complicating an acute infectious disease is suggested, but considered less likely.

Serial electrocardiograms during various stages of mumps are recommended to establish the incidence of cardiac complications and the optimal period for complete convalescence. Since mumps myocarditis can precede the parotitis, the mumps complement fixation and intradermal tests are suggested as diagnostic aids in obscure myocarditis. Results of serial transaminase terminations were within normal limits, which is probably compatible with the presence of superficial interstitial involvement of the myocardium.

Corticosteroid therapy is probably not indicated in uncomplicated mumps myocarditis, which usually does very well on convalescent bed-rest therapy alone. However, in the presence of additional factors, such as mumps orchitis, pancreatitis or other complications, such steroid therapy may be considered. S. J. SHANE

Eradication of Focal Infection in Diffuse Glomerulonephritis: Causes of Failure *(in German).*

R. HEINTZ AND P. CHRIST: *Deutsche med. Wchnschr.*, 83: 2239, 1958.

Although eradication of focal infection is still considered to be indicated in acute diffuse glomerulonephritis, the eradication can, in rare cases, lead to aggravation and even to death. Of 62 cases of this disease observed in four years at the University Hospital in Frankfurt, two patients died, one after tonsillectomy six weeks after onset of an acute glomerulonephritis; the other developed eight days after tooth extraction a typical glomerulonephritis with oliguria and died on the 14th day of illness. In spite of this, infected foci should be removed if recovery is delayed more than six weeks at the latest, and if there is no evidence of irreversible renal damage, especially albuminuria and hæmaturia. Mild transient exacerbation of the nephritis is not infrequent, but proper preparation with antibiotics and reduction of reactivity with calcium, antihistaminics and corticosteroids will prevent more serious complications.

In subacute or chronic nephritis, removal of infected foci is usually useless; this finding is in agreement with the titre of streptococcus antibodies (antistreptolysin, etc.) in these patients, which is very rarely elevated. Recent investigations have disclosed that persistence of glomerulonephritis and its transition into the chronic form are independent of streptococcal infection. Investigations quoted by the authors point to the importance of antibody reactions in this condition, with the development of auto-antibodies against one's own renal protein. Other experiments are quoted which show that elevation of temperature and other non-specific stimuli may provoke an anamnestic reaction leading to an increase of antibodies. This would explain the frequently observed aggravation of pre-existing chronic glomerulonephritis after tonsillectomy or other attempts to eradicate focal infection.

W. GROBIN

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Electrocardiogram in Neurocirculatory Asthenia (Anxiety Neurosis or Neurasthenia).

W. B. KANNEL, T. R. DAWBER AND M. E. COHEN: *Ann. Int. Med.*, 49: 1351, 1958.

The histories of 24 adults, who had been studied consecutively in the Framingham Heart Disease Epidemiology Study, were examined to determine whether neurocirculatory asthenia was associated with electrocardiographic (ECG) abnormalities. The diagnosis of neurocirculatory asthenia was based on the history of subjective symptoms, according to criteria previously formulated. The ECG's were interpreted according to currently accepted criteria. A summary of both these sets of criteria is presented in the paper. After the exclusion of subjects with cardiovascular disease or hypertension, the remaining series for the present study consisted of 203 patients with neurocirculatory asthenia and 757 normal control subjects. A meticulous examination of ECG's of these two groups revealed that the same types of ECG abnormality occurred in patients with neurocirculatory asthenia *and in controls.* Even the frequency of these abnormalities was the same. No ECG configuration was recognized that could characteristically be associated with neurocirculatory asthenia.

It was concluded that ECG abnormalities indicating the presence of heart disease do not occur as the result of neurocirculatory asthenia. Furthermore, when significant ECG abnormalities occur, they should be interpreted without reference to co-existing symptoms of neurocirculatory asthenia. S. J. SHANE

Necropsy Evaluation of Gas-Contrast Roentgen Visualization of Liver and Spleen.

S. ZELMAN: *Am. J. M. Sc.*, 236: 747, 1958.

Roentgen visualization of the liver and spleen can be obtained by gas contrast, in the erect position, after inflation of the stomach by Seidlitz powder and the colon by air. Autopsies were carried out on 20 patients so examined, within three months of the examination. Statistical correlations were obtained between x-ray measurements of the liver and spleen and their weight at autopsy. Though a number of variables interfered with correlation, the coefficients obtained proved comparable to those between x-ray measurements of the heart and its weight at necropsy. It is concluded that x-ray measurements of liver and spleen obtained with the gas-contrast method warrant the degree of clinical confidence accorded x-ray visualization of the heart. S. J. SHANE

Problem Cases of Peripheral Vascular Disease *(in German).*

H. GESENIUS: *Deutsche med. Wchnschr.*, 84: 13, 1959.

The author developed a bilateral oscillograph during World War II, when he used it for evaluation of vascular injuries in soldiers. Ten years ago, he first published his observations; since then, this instrument has been used by many workers. The present report confirms the value of bilateral oscillography in diagnosing obscure or doubtful cases of peripheral vascular disease. Several cases are presented in which palpation failed to disclose any difference between two extremities but the instrument clearly demonstrated diminished pulsation in one limb. On the other hand, its use excluded suspected arterial insufficiency in another case and obviated surgical intervention for suspected arterial embolism. W. GROBIN

Essential Emphysema—A Questionable Diagnosis *(in German).*

W. HADORN: *Deutsche med. Wchnschr.*, 84: 213, 1959.

The changes which have taken place during the last decades in the understanding of the pathogenesis of so-called essential emphysema are reviewed. Exact pulmonary function tests enable us to diagnose emphysema at the bedside. Irrespective of the underlying condition, emphysema is always associated with an increased residual lung volume. This is usually preceded by decreased forced expiratory volume, which is in turn due to bronchiolar obstruction. All the non-obstructive forms of alveolar emphysema are mild and are in themselves not of clinical significance. Obstructive emphysema is due to bronchial asthma or to chronic bronchitis. Often slight degrees of bronchospasm may go unnoticed even by the patient for years; only pulmonary function tests will uncover the delay in expiration and decrease in forced expiratory volume.

Prevention of emphysema aims at energetic treatment of asthma by conventional methods which include physiotherapy and, in severe cases, ACTH and corticosteroids. Chronic bronchitis was found to be associated with *H. influenzæ* in the sputum in some 90% of cases. Persistent treatment with antibiotics, especially chloramphenicol, for weeks and months may be necessary to eradicate the infection. The significance of emphysema and the need for its prevention and treatment are discussed in the light of our aging population and the increasing number of chronic pulmonary invalids.

W. GROBIN

Graded Pulmonary Vascular Changes and Hæmodynamic Findings in Septal Defect and Patent Ductus Arteriosus.

D. HEATH *et al.*: *Circulation*, 18: 1155, 1958.

Studies are presented from 15 cases of atrial septal defect, 19 cases of ventricular septal defect, and six cases of patent ductus arteriosus, and results of cardiac catheterization are correlated with graded changes in the pulmonary arterial system, obtained by histological study. From the correlations it is concluded that a grading system is valid as an estimate of those factors which determine the type of resistance to flow through the pulmonary vascular bed. It should be realized, however, that in the very young the normal pulmonary vascular bed has a high resistance.

In this scale, grades 1 to 3 indicate a vascular bed which, though it may maintain a moderately high resistance, is labile. Grades 5 and 6 indicate a vascular bed that maintains a high resistance and that is no longer labile. Grade 4 seems to represent a transitional stage between these two types of vascular beds. S. J. SHANE

Course of Primary Hypertension in the Young.

G. A. PERERA: *Ann. Int. Med.*, 49: 1348, 1958.

There are indications that primary (essential) hypertension frequently commences in the early phases of adult life, and certain authors have suggested that the course of the illness is more rapid when it begins at an early age.

Thirty patients were studied in whom "established" diastolic hypertension had been present from the age of 25 years. Patients with secondary hypertension were excluded from this series. Eight patients died after a median survival period of 21 years (with extremes of 10 to 40 years). The other 22 patients

remained under observation for a median period of 20 years (with extremes of 10 to 37 years). The data obtained in this study emphasize again the fact that the initial level of the casual blood pressure cannot be correlated with rapidity of progression of the hypertension. Furthermore, the data suggest that the course of primary hypertension is not necessarily more rapid in younger patients than in older ones.

S. J. SHANE

SURGERY

Carcinoma of the Stomach.

C. E. WELSH AND E. W. WILKINS, JR.: *Ann. Surg.*, 148: 666, 1958.

At the Massachusetts General Hospital, an improvement in the five-year survival rate has been shown in those cases of carcinoma of the stomach seen since 1946 and up to 1953. A study of these 380 cases (13% five-year survival) was made.

Lymph node metastases were an important influence on prognosis, for 51% survived after resection for cure if no lymph node metastases were seen, while 17% survived when nodes were positive. Microscopic cancer at the resection margin was a bad omen, with only one five-year survival. Ten out of the 380 were operated upon for benign ulcer but found to have cancer and 50% survived five years. Seven had pernicious anæmia and 29% survived. Ten had gastric polyps and 40% survived.

Compared with the previous average delay of five months in seeking advice, the time from onset of symptoms in this series averaged four months, and this is thought to be an important gain. Operation was performed in all but 8.5% of the series: exploration only in 16%, palliative operations without resection in 7%, palliative resection in 24% and resection for cure in 43%. Operative mortality was higher than previously because resection was more frequent and more extensive, often including pancreatectomy: total extended gastrectomy showed a 15.4% mortality.

The surgeon's judgment is important in the decision in each case as to whether the higher operative mortality associated with extensive operations is justified. Often subtotal distal resection gives the best result: 47% of patients in whom these were performed for cure survived five years, and if the nodes were negative, 63%. Small cancers obstructing the cardia, especially in a hiatus hernia, may well be treated by proximal subtotal gastrectomy. BURNS PLEWES

Giant Cell Tumour of Bone.

B. L. COLEY, N. L. HIGINBOTHAM AND T. KOGURE: *Am. J. Surg.*, 96: 479, 1958.

The clinical, radiological and histological features of giant cell tumour of bone are so characteristic that for over a hundred years it has been considered a definite entity. However, in view of the difficulty in interpretation of certain cytological variations, a difference of opinion exists as to the best treatment.

Attempts have been made to classify these into three grades depending on histology, but previous studies have shown a tendency for some of the least aggressive types in time to undergo malignant transformation. The authors agree with those who maintain that it is not possible to predict the ultimate outcome of a case from study of the initial histology of the tumour. As is generally accepted, it is most common in the third and fourth decade, with a slight preponderance among females. The majority occur in the epiphysis of the upper end of tibia, lower end of femur or radius, extending to the adjacent metaphysis in many cases. Radiographs usually show a circumscribed osteolytic area, sometimes with trabeculations, giving a compartmental appearance.

Aspiration biopsy is recommended as very reliable. Open biopsy should not be done without proceeding to cavity cauterization with zinc chloride and packing with bone chips.

The benign lesion may respond to local surgical measures or to radiation. On the other hand, it may recur after treatment with either of these methods or combinations of them. This study would suggest that there is no evidence that radiation therapy can control a malignant giant cell tumour, whereas resection after tumour has recurred following primary radiation is sometimes successful. In an area where it is possible, primary resection for a giant cell tumour probably deserves a wider employment than curettage because, after resection, the recurrence rate is low whereas with curettage it is comparatively high.

Six interesting case histories are presented along with some very good illustrations.

ALLAN M. DAVIDSON

Leiomyoma of the Duodenum.

W. N. COOMBES: *Brit. J. Surg.*, 46: 127, 1958.

In reporting a case of smooth muscle tumour of the duodenum from Ottawa, the signs and symptoms that made a preoperative diagnosis possible are listed. Hæmorrhage into the tumour probably explains a very short history of pain, fever, and some disturbance of micturition by congestion of the adjacent ureter. Melæna is often found with leiomyoma of the intestine. X-ray findings suggested a tumour of the duodenum extending into the retroperitoneal space.

Differentiation of benign from malignant smooth muscle tumours may be difficult, but even if frequent mitotic figures are found in the section, long survival can be expected after successful resection.

BURNS PLEWES

Permeability of Cerebral Blood Vessels in Healing Brain Wounds.

J. LEE AND J. OLSZEWSKI: *Neurology*, 9: 7, 1959.

Radioactive iodinated bovine albumin was injected into rabbits at various time intervals after producing cortical coagulation of the brain. Increased permeability of the damaged area as evidenced by intense radioactivity in the autoradiographs was similar in distribution to that of œdema of the brain. After the fourth day, the damaged area was becoming less radioactive, and finally the radioactivity confined itself to the border of necrosis and neighbouring meninges. Using the method described in this paper, the authors were unable to observe any radioactivity in the healthy meninges and brains of rabbits, nor did spontaneous encephalitis found accidentally in several rabbits produce radioactivity in relation to the lesions.

The œdema was localized almost exclusively in the white matter, indicating that increased permeability of the cerebral blood vessels was the predominating mechanism in the production of this œdema. Changes of osmotic pressure of the blood or of the tissues, which are responsible for œdema production in other conditions, did not seem to be of importance in this series of experiments. W. GROBIN

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Treatment of Paralytic Ileus Without Use of Gastro-intestinal Suction.

A. GERBER, F. A. ROGERS AND L. L. SMITH: *Surg. Gynec. & Obst.*, 107: 247, 1958.

The authors have treated 1000 patients with paralytic ileus successfully without nasogastric suction. These cases included all types of stomach, colon and biliary tract surgery. It is their opinion that not only is nasogastric intubation unnecessary in most instances, but that the patient is made uncomfortable, electrolyte replacement is a more difficult problem, and morbidity is increased – primarily by respiratory complications.

They believe that the small amount of fluid obtained by suction was insignificant compared with the large volumes secreted and reabsorbed in the gastro-intestinal tract. Similarly, swallowed air was not considered a problem, provided the patient was given absolutely "nothing by mouth".

The non-intubated patients recovered from the ileus as quickly as those in the control series, and the morbidity in this group was distinctly decreased. Maintenance of fluid and electrolyte balance was simplified, as was nursing care. JOHN A. PALMER

Intraperitoneal Neomycin in Treatment of Acute Bacterial Peritonitis.

H. G. GREENE: *Surg. Gynec. & Obst.*, 107: 169, 1958.

Pridgen, Engel and Denson have reported respiratory arrest after intraperitoneal administration of neomycin, but massive doses of the drug were given in their cases. Schatter has shown that neomycin used intraperitoneally is a potent bactericidal agent, with a wide spectrum, and is relatively non-irritating to tissues.

Greene treated 20 patients with acute bacterial peritonitis by Schatter's method. Two fine polyethylene catheters were inserted through the abdominal wall during operation by threading them through a No. 13 needle. The tip of one catheter was placed just superior to the contaminating lesion and the tip of the other in the pelvis. Neomycin, 0.125 to 0.250 g. in saline, was injected every six hours for 48 hours after operation.

It was felt that the expected mortality rate in this series was reduced by using this method as an adjunct to surgical treatment and antibiotics by the usual routes. The drug should be given in moderate-sized, divided doses and the amounts given to children and debilitated patients decreased proportionately.

JOHN A. PALMER

The Intestinal Factor in Irreversible Endotoxin Shock.

R. C. LILLEHEI AND L. D. MACLEAN: *Ann. Surg.*, 148: 513, 1958.

An investigation of irreversible shock in dogs involved a series of experiments in which the endotoxin obtained from Gram-negative bacteria and lethal to normal dogs was the agent used to evaluate various treatments. The principal autopsy finding in either hæmorrhagic or endotoxin shock is hæmorrhagic necrosis of the bowel mucosa. This is prevented in hæmorrhagic shock by pretreatment with adrenergic blocking agents. Vasospasm of small arteries and veins is supposed to be the cause of the bowel necrosis in endotoxin shock also. These changes in the dog mesentery and intestine are described as the sympathomimetic endotoxin is administered.

The administration of chlorpromazine and Dibenzyline protected the animal by the blocking of the sympathomimetic effect. The removal of most of the intestine increased survival time even though the bleeding diathesis was uncontrolled. Hydrocortisone also enabled the survival of 90% of the animals, apparently protecting against the effects of prolonged vasoconstriction or decreasing the intensity or duration of the vasospasm.

On the other hand, no benefits from the use of intestinal antibiotics could be demonstrated. Bowel sterilization does not appear to prevent the development of irreversible hæmorrhagic shock. Nor did hypothermia improve the rate of survival in endotoxin shock. The use of metaramol and norepinephrine hastened the effect of the endotoxin: both are also sympathomimetics. BURNS PLEWES

OBSTETRICS AND GYNÆCOLOGY

Production of Congenital Malformations by Dietary Measures.

J. WARKANY: *J. A. M. A.*, 168: 2020, 1958.

Under strict experimental conditions it was possible to induce in rats a syndrome of skeletal malformations by maternal riboflavin deficiency. Shortness of the tibia, fibula, radius, ulna, and mandible, fusion of the ribs and cleft palate were found in about one-third of the young. Malformations of the eyes, the great vessels, the heart and the kidneys were induced by keeping the mother rats on a vitamin A deficient diet. Experiments are also quoted in which a high incidence of hydrocephalus in infant rats resulted from deficiency of folic acid and cyanocobalamin in the maternal diet, and exencephaly and ocular defects resulted from pantothenic acid deficiency. Vitamin E deficiency in pregnant rats results in fetal absorption, but if the deficient diet is supplemented with vitamin E in midpregnancy some of the fetuses are salvaged and they are born alive but with malformations.

Feeding of antimetabolites to pregnant rats produced more pronounced deficiencies in very few days and resulted in the induction of these malformations in the young in a much higher proportion of cases. Aminopterin, a folic acid antagonist, was observed to have produced hydrocephalus, meningo-encephalocele, harelip, and cleft palate in human embryos whose mothers had taken the chemical to induce therapeutic abortion. Hypervitaminosis A produced in pregnant rats resulted in many malformations in the young, mainly skeletal but also of eyes and brain. Differences in malformations in different strains of mice are of interest. Feeding diets deficient in riboflavin but with added galactoflavin to pregnant mice produced atresia of the œsophagus in 80% of the young of two strains but in only 2% of another strain. In one strain, maternal fasting for 24 hours on the ninth day of pregnancy produced exencephaly, vertebral anomalies and fused ribs in 28% of the offspring.

These experiments do not prove that congenital malformations in man are due to maternal dietary deficiencies, and various reasons are given why it would be hazardous to equate these animal experiments with human conditions. On the other hand, maternal iodine deficiency is blamed for endemic cretinism, and it as well as endemic goitre disappears when iodized salt is given to people in iodine-poor regions. Antimetabolites could be teratogenic in man, and anorexia, vomiting or lack of food can in rare cases cause conditions in women similar to those in the animals cited above.

Deficiency of some of these well-defined chemical compounds, which are known constituents of enzymatic systems, may influence genetic mechanisms generally assumed to be mediated through enzymatic activity.

W. GROBIN

Prolonged Pregnancy Syndrome.

J. WALKER: *Am. J. Obst. & Gynec.*, 76: 759, 1958.

The existence of the prolonged pregnancy syndrome must be acknowledged. The outlook of each obstetrician will be modified by the type of his practice and by his own experience. There is no magical significance about the 280th day or the 282nd day, or the 290th day. There is, however, an increasing problem as pregnancy becomes prolonged after about the 39th week, which is a different problem from those which confront the obstetrician, the mother, and the baby before that time. It has always to be remembered that, despite a low mortality, the baby from the prolonged pregnancy will be more liable to oxygen deficiency indicated by fetal distress and be called upon to withstand a difficult labour. Both these factors, often additive, may cause minor damage with permanent sequelæ.

ROSS MITCHELL

PÆDIATRICS

Acute Laryngo-Tracheo-Bronchitis: 122 Cases Studied in the Hospital for Sick Children, Toronto.

ANN M. PEACH AND ELISABETH ZAIMAN: *Brit. M. J.*, 1: 416, 1959.

Of the 122 cases of acute laryngo-tracheo-bronchitis admitted during the two winter periods of 1952-53 and 1953-54, 38 were severe enough to require tracheotomy. Medical treatment consisted of placing the child in a "croupette" in which 100% humidity was maintained by air or oxygen vaporizing water through a nebulizer. Adequate hydration, mild sedation and penicillin, alone or in combination with streptomycin, were the usual measures. Whilst in a previous series for 10 years up to 1944 the overall mortality was 20%, and 9.2% in 1944, the mortality in the present series was 0.8%. Patients ranged in age from 4 months to 10 years, with one-third of the total in the 1-2 year age group. The authors believe that falling temperature associated with falling humidity in the thermostatically controlled Canadian homes produces drying of secretions and helps the development of mechanical obstruction of the respiratory tract in the presence of infection.

W. GROBIN

ORTHOPÆDICS

Treatment of Tennis Elbow (Epicondylitis) by Denervation.

E. B. KAPLAN: *J. Bone & Jt. Surg.*, 41-A: 147, 1959.

The pathological changes associated with the triad of symptoms in this condition—i.e., pain over the lateral epicondyle, pain on extension of the thumb and wrist, and weakness of hand grasp—are unknown. In an attempt to ascertain the cause for frequent failure in these cases, the author carried out detailed dissections of the area in 30 adult elbows. As a result, he advocates a partial radial neurectomy. The branches concerned originate from the main trunk of the radial nerve about 1-2 cm. distal to the nerve of the brachioradialis. This in turn arises 4-5 cm. distal to the emergence of the radial nerve proper from the posterior compartment of the arm in the interval between the biceps and the brachioradialis. A detailed anatomical account is given of all the branches and relations of the radial nerve in this region, as well as those of the musculo-cutaneous nerve, which is an important point of reference in this operation.

As a preliminary test for probable effectiveness, the area is blocked with procaine by directing the needle into the region at a point just medial to the brachioradialis, on the bi-epicondylar line.

The operation itself is a straightforward anatomical dissection through the plane between the brachioradialis and the biceps muscles. These are separated after sectioning the deep fascia just lateral to the musculo-cutaneous nerve. It is claimed that the identification of the branches concerned is not difficult, and that there have been no recurrences in the three patients treated by this method.

ALLAN M. DAVIDSON

Advantages of Early Spine Fusion For Fracture-dislocation of the Cervical Spine.

H. F. FORSYTH *et al.*: *J. Bone & Jt. Surg.*, 41-A: 17, 1959.

This study is based on a statistical analysis of 84 cases of fracture-dislocation of the cervical spine treated by the authors, both conservatively and by fusion. During the past 20 years, more and more reports have appeared, indicating the desirability of this method along with skull traction with tongs to offer the best protection in early and definitive treatment of these cases.

It is now evident that hyperextension, either with or without a rotary element, is frequently the causative mechanism, rather than flexion as previously thought. Time spent at the very outset to determine the exact details of the accident may be helpful. This type of stress is prone to cause fractures of the posterior bony structures, which are frequently multiple. Following this, in many the vertebral body may be displaced anteriorly. In rotatory hyperextension fracture-dislocations, each vertebra is forced backward and downward towards the opposite side on its fellow below, until something gives way. This is usually in the more mobile segment, i.e. fourth, fifth, and sixth cervical vertebræ.

Extreme caution to avoid aggravating the condition is stressed. If cervical spine injury is suspected, 5-7 lb. of head-halter traction should be applied immediately, even before x-ray examination. If it is obvious that injury in this region has occurred, especially if neurological signs are present, 15-20 lb. of skull traction is applied by means of Crutchfield tongs. Up to twice this weight may be necessary to obtain reduction. Serial roentgenograms are made at short intervals of 15-30 minutes to check progress. Straight traction initially is changed to the hyperextension position after reduction in the flexion type of fracture-dislocation.

As the primary purpose is to protect the cord and nerve roots, it is desirable to stabilize those fractures in which residual or recurrent deformity might occur and jeopardize the neural elements. Fractures of the odontoid process, or one or both articular processes of this or other vertebræ, are difficult to immobilize.

A patient with an uncomplicated injury should be ready for fusion within one week. Immediate operation may be necessary if there is a persistent block on spinal tap, and the myelogram shows pressure on the cord. Two different procedures are used, depending on the level and type of fracture. If it is necessary to inspect or decompress the cord, laminectomy may be

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done at the time. Care to avoid pressure and force is important in preparing the laminæ, etc., for the graft.

For a fracture of the odontoid process or tearing of the transverse ligament with atlanto-axial dislocation, wiring and fusing of the three cervical vertebræ are advocated. A wire is passed under the centre of the posterior arch of the atlas and fastened tightly around the tip of the spinous process of the axis. Two pieces of rib or other cortical bone are fixed in place by 20-gauge stainless steel wire passed under the laminæ on each side of the first three cervical vertebræ. In fractures below the axis the wires pass under the base of the spinous process of the lowest fractured vertebra, and then through holes made near the top of the base of the spinous processes of the next two vertebræ. Such spinal fusions appear to be solid in four to six months.

A comparison of results of 38 spine fusions and 46 injuries treated conservatively would suggest that the former group had less residual deformity and a lower recurrence rate. These patients spent less time in hospital or in uncomfortable casts and were able to return to work sooner. ALLAN M. DAVIDSON

Anticoagulant Therapy: Clinical Experience With Acenocoumarin (Sintrom) and Other Coumarin Derivatives.

Y. DESROCHERS, N. AÉRICHIDÉ AND P. DAVID: *Am. Heart J.*, 57: 321, 1959.

Of 382 patients on anticoagulant therapy 305 received acenocoumarin, 40 bishydroxycoumarin, and 37 ethyl biscoumacetate (Tromexan). An induction dose of 11-25 mg. of acenocoumarin reduced prothrombin values to 50-60% within 18-60 hours, and on a maintenance dose of 3.6 mg. very stable levels of hypoprothrombinæmia were achieved over an indefinite period of time. The incidence of hæmorrhagic episodes per patient per year of therapy was found to be 0.6 with acenocoumarin, 2.1 with dicoumarol and 2.9 with Tromexan. Acenocoumarin is considered preferable to other coumarin derivatives but should be used in smaller doses than usually recommended, especially in the presence of cardiac or renal failure. A mortality of 7.6% in this group of patients, most of whom had coronary artery disease, over a period of 650 treatment months is considerably lower than in similar groups of cardiac patients who have not received anticoagulant treatment. W. GROBIN

INDUSTRIAL MEDICINE

Occupational Medicine—Whither and How!

R. A. KEHOE: *J. Occup. Med.*, 1: 1, 1959.

Occupational medicine has attained adult status within the past two decades. Significant features of its development and achievements are discussed.

The general concern of organized medicine throughout the United States in the field of occupational medicine is expressed by the activities of such organizations as the Industrial Medical Association, the American Academy of Occupational Medicine, the Council on Industrial Health within the American Medical Association, and the American Industrial Hygiene Association. Reference is made also to the American Board of Preventive Medicine, within which occupational medicine has achieved formal recognition as a specialized field of practice.

Facilities for medical and hygienic research in industrial health, almost negligible in the early quarter of this century, have advanced rapidly. Today interest is widespread among representatives of industry, government and the professions involved. Of equal significance has been the growth of the literature dealing with occupational medicine and hygiene. Furthermore, graduate training in occupational medicine is now offered in conventional form in several approved schools of medicine and public health in the United States.

As yet, however, these adaptations of medical research, education and practice to the contemporary needs of an industrial and urban society are most inadequate. The physical background of modern industry contains a multitude of unexplored and insidious dangers. The great proportion of American industrial organizations operate almost entirely without benefit of expert guidance in preventive medicine and industrial hygiene. Only a minute proportion of industrial organizations have valid medical information concerning the health of their employees.

In matters of industrial hygiene, federal, state and municipal health agencies together with professional personnel have, through guidance, supervision and regulatory mechanisms, made a considerable contribution to the health of the working population. This, however, is not equal to that which could be reached by direct efforts of industry in behalf of its own employees. It must be decided whether the responsibility of the future is to be assumed and met by industry with ample professional guidance and service, or by government.

Certain solutions are considered: (1) increased recruitment, training and research to provide a medical profession competent to accept responsibility for the direct handling of industrial health; (2) increased number of industrial hygiene engineers within industrial organizations to work with physicians in coordinated effort; (3) adoption of a program of supervision and regulation of industry, in hygienic matters, by the individual states, following the general pattern of Great Britain in establishing the system of medical and lay inspection of factories.

In the author's opinion none of these would be entirely satisfactory. The best method of attaining adequate coverage within and throughout American industry is the logical extension of the valid achievements so far attained. MARGARET H. WILTON

ERRATA

In the article "Analysis of Intrauterine Malformations of the Vertebral Column Induced by Oxygen Deficiency" by K. H. Degenhardt and E. Knoche, published in the issue of March 15 (80: 441, 1959), the following corrections should be made:

Page 441, line 2, right-hand column: "searches of the teams led by Prof. *Buechner* in".

Page 441, line 22, right-hand column: "by benzyl alcohol, of the 145 litters containing *674*".

Page 444, line 10, left-hand column: "from the top on the *right*-hand side, the increase of".

Page 444, line 16, left-hand column: "*right* of the picture are two primi-".

Page 444, line 9, right-hand column: "*cranial edge.* Notice the malformed".

Page 444, line 30, right-hand column: "lies a *symmetrical*, cleft vertebral".

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BOOK REVIEWS

PSYCHIATRY AND THE PUBLIC HEALTH. G. R. Hargreaves, Nuffield Professor of Psychiatry, University of Leeds. 118 pp. Oxford University Press, London and Toronto, 1958. $2.00.

When the Heath Clark Lectures were established in the London School of Hygiene some years ago, with the proviso that each lecturer should talk about the history and progress of preventive medicine, it is unlikely that the benefactor whose bequest provided the funds envisaged the possibility of a psychiatrist's contributing to the series. But with the control of infections and the lessening in gravity of many other traditional subjects dealt with in public health, mental health of the population has come to the forefront. Professor Hargreaves, whose five lectures constitute the present volume, is very well qualified for his task, since his energy and vision did much to promote the mental health program of the World Health Organization.

In his first lecture, Hargreaves traces the history of the various parts of psychiatry, showing how these grew up from various origins and from associations with completely different types of institution. For example, he traces the history of child guidance from an interest in juvenile delinquency. In his second lecture, on psychiatry in society, he shows how the psychiatrist has had to turn to sciences outside the specifically medical ones for help, while in the third lecture on psychiatry and medical administration he examines the deplorable division of authority in mental health matters in the United Kingdom.

In his fourth lecture, Hargreaves examines the relationship of psychiatric treatment to the family doctor, explaining carefully the difficulties which lie in the way of adequate instruction of the medical student in psychiatry, but affirming his belief in the absolute necessity ultimately of giving students a good grounding in psychiatric skills. Lastly, he examines the relation of psychiatry to the whole practice of public health, with considerable emphasis on Britain. While some of the material contained in these lectures is applicable mainly to the United Kingdom and the National Health Service, much of the material is worthy of study in Canada, for many of the points made by Hargreaves are of universal applicability. It remains to be added that the author writes clearly and forcefully and that the lectures are a joy to read.

AN ATLAS OF ESOPHAGEAL MOTILITY IN HEALTH AND DISEASE. Charles F. Code, Mayo Clinic, and others. 134 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $9.25.

A group of physiologists and physicians at the Mayo Clinic have been studying the motor activity of the human œsophagus for seven years. Tiny electromagnetic transducers were utilized to record intraluminal pressures at various levels both at rest and during swallowing. This atlas was produced when the authors became convinced that the records tell the story themselves much better than the written word. It is certainly true that with a minimum of text the tracings reproduced here give a very clear picture of œsophageal motility and particularly of the pharyngo-œsophageal and gastro-œsophageal sphincters. The œsophagus has been studied in healthy individuals for comparison with three disease conditions—achalasia, diffuse spasm, and scleroderma. It is to be regretted that no investigations of hiatus hernia patients are reported.

This atlas is a major contribution to the study of œsophageal function.

THE EPILEPTIC SEIZURE. Its Functional Morphology and Diagnostic Significance. A Clinical-electrographic Analysis of Metrazol-induced Attacks. Cosimo Ajomone-Marsan and Bruce L. Ralston, Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, Bethesda, Md. 251 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1957. $6.50.

This book presents a clinical and electrographic analysis of Metrazol-induced seizures. The authors have attempted to study the pattern of epileptic seizures including the pre-ictal, ictal and post-ictal clinical symptoms. These are discussed and integrated with their electrographic correlates.

The problem of cortical and subcortical pathways for the spread of activation is discussed, as are some of the problems related to temporal lobe attacks.

The book is of interest to all who are concerned with the study of epilepsy and brain physiology. It represents a valuable contribution to the clinical and physiological studies of the epileptic seizure.

THE NEUROLOGIC EXAMINATION. Incorporating the Fundamentals of Neuroanatomy and Neurophysiology. Russell N. DeJong, University of Michigan Medical School. 1078 pp. Illust. 2nd ed. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York, 1958. $20.00.

This is a second edition of a comprehensive book which incorporates the fundamentals of neuroanatomy and neurophysiology with clinical neurology. There are detailed descriptions of various diagnostic procedures, which in turn are correlated with their clinical application and significance.

Some of the newer physiological concepts have been incorporated in this second edition and the book retains its complete and thorough form. This volume should continue to be valuable for reference and study by any physician who has an active interest in neurological methods and problems.

DISEASES OF THE LIVER AND BILIARY SYSTEM. Sheila Sherlock, University of London, England. 719 pp. Illust. 2nd ed. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $13.75.

In the second edition of this book the author has made numerous modifications to keep pace with recent knowledge and yet has not lengthened the text. Important changes are to be found in the sections dealing with hepatic coma and jaundice respectively. The chapter describing the investigation of portal hypertension and assessing the various surgical procedures designed to lower the pressure is of particular value.

Thirty-seven new figures have been added to this already well illustrated book. The author, in an attempt to cope with the extensive literature in the field, has found it necessary to list 500 new references.

Dr. Sherlock has again produced a clear, readable and authoritative book which should prove most useful to either student or physician.

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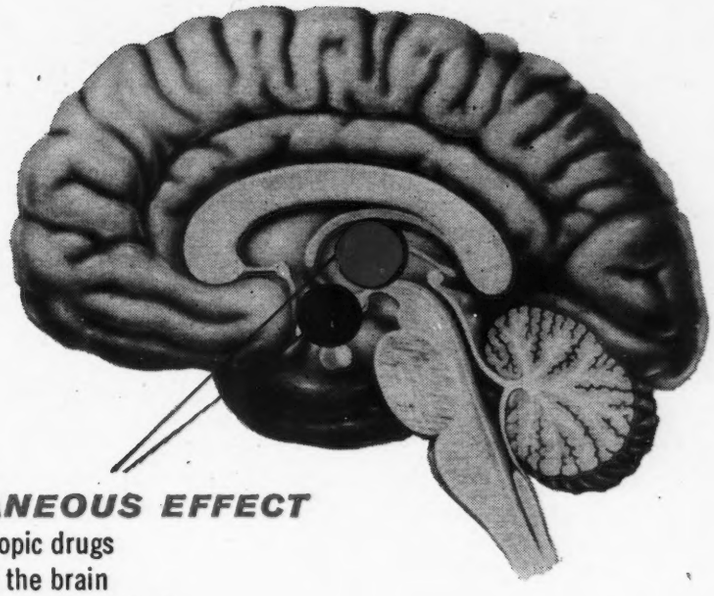

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PSYCHOPHARMACOLOGY. Pharmacologic Effects on Behavior: Vol. III, Progress in Neurobiology. Edited by H. H. Pennes, New York. 362 pp. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York, 1958. $8.00.

This is the third volume in a series called *Progress in Neurobiology,* these volumes covering progress in basic neurological sciences and disciplines. This book contains the proceedings of a symposium on effects of drugs on behaviour in which 41 scientists of different neurological disciplines attempted to synthesize, in a multidisciplinary survey, much of what is currently known of the subject.

In 13 excellent papers they have attempted to cover the biochemistry and the effects on brain metabolism *in vitro* of some of the tranquillizing drugs, the biochemistry of hallucinogens, the serotonin theory of psychotomimetic action, effects of various drugs on escape and avoidance behaviour; and, in one paper by Lawrence Kubie, some methodological considerations from the viewpoint of clinical analysis of the investigation of the pharmacology of psychological processes.

The papers are excellent; the discussion is at times stimulating. The book suffers, as do all books of this kind, from the inevitable spottiness and lack of cohesion of different authors presenting their own ideas. But despite this unavoidable shortcoming, the book is an excellent contribution on the knowledge in these areas.

Of particular interest are the papers: *The Biochemistry of Hallucinogens,* by Lajtha; *The Neurologic and Psychiatric Changes Related to Serotonin,* by Woolley, presenting the essence of his theory; *Biochemistry of the Tranquilizing Drugs,* by Strecker; *Relation of Drugs to Reaction Components in Subjective Responses,* by Beecher. Kubie's paper is a masterpiece of thinking and writing. The reviewer's favourite is the paper by Murray Jarvik, *Are There Any Psychotherapeutic or Psychotomimetic Drugs?* This paper is a very erudite and clear analysis of the difficulties of classification, and a masterpiece of scientific reasoning and clarity of thought. The doubts he raises as to certain aspects of the alleged efficacy of these drugs are too little thought of, or considered, by the majority of physicians.

This book is of particular value to the neurologist, pharmacologist, psychologist and psychiatrist, but is of general interest to all interested in the specifically pharmacological effects of the new drugs on the function of the C.N.S.

NEW PRIMER ON ALCOHOLISM. Marty Mann. 238 pp. Rinehart & Co. Inc., New York; Clarke Irwin & Co. Ltd., Toronto, 1958. $2.95.

Many physicians will welcome this brief, sensible and eminently practical work on alcoholism which can be safely recommended to those needing information about this great illness. It will be useful not only to alcoholics themselves, but to their families, relatives, friends, and also to police, social workers, lawyers, magistrates and employers who find themselves baffled and frustrated by this widespread and often misunderstood ailment. Mrs. Marty Mann has written a book designed to meet this demand. She is well qualified to do so, because after her own recovery from alcoholism in 1939, she trained at the Yale School of Alcoholism Studies, becoming after this the founder and Executive Director of the National Council of Alcoholism in New York. This body offers widespread advisory services to alcoholics, their families, relatives and friends. It also backs research work.

Mrs. Mann's approach is wisely the middle of the road. She is not an extremist. She emphasizes that alcoholism is a disease which afflicts a limited but large number of people. These people are very sick and require treatment. While the current evidence suggests that the illness has its basis in some hormonal abnormality, it is undoubtedly precipitated, sustained and aggravated by psychosocial difficulties.

The first step in dealing with any disease is to realize that it is a disease and not a sin. It must then be recognized, which means classifying its course and symptoms. Once this has been done, the possibility of directed medical intervention of many sorts arises. However much medical skill is available, it will be of no use unless the sick person comes or is brought to the physician for treatment. In alcoholism, unlike some other illnesses with grave social consequences, much of the onus lies upon the sick person to secure treatment. Unluckily for a variety of reasons, most of them social, alcoholics are frequently unable to understand that they are ill and need treatment. Mrs. Mann properly gives plenty of space to discussing how they can best be encouraged to do so, and the mistakes that are so easily made by desperately worried spouses, relatives and over-anxious friends. The best of many first-class chapters is probably that on "what to do about an alcoholic".

On second thought your reviewer feels that although this book is primarily intended for medical laymen, it is well worth any physician's time. In addition to giving an excellent survey of current views about alcoholism, there are many useful hints as to how we can benefit our alcoholic patients by persuading them that they are sick and can be helped by medical treatment.

DISEASES OF THE EXTERNAL EAR. Ben H. Senturia, Associate Professor of Clinical Otolaryngology, Washington University School of Medicine. 211 pp. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1957. $9.25.

The author has had an extensive experience with external ear diseases, and is highly qualified to deal with the problem. Because many people receive incorrect or inadequate treatment, a guide like the present work should serve a highly useful purpose. "This is a report of approximately five years of co-ordinated laboratory and clinical research oriented to throw some light on this widely prevalent and aggravating group of diseases." Consideration is given to the prophylaxis of external otitis. It provides the otolaryngologist, dermatologist and general practitioner with effective, proven therapeutic techniques which the author has found successful in treating diseases of the external ear. There is no doubt that Senturia has made some substantial contributions to our knowledge of external ear diseases. It is only in natural sequence that he should want to compile his material as a permanent record. The physician who encounters external ear diseases in his practice can enlighten himself in every aspect of them by a careful perusal of this important work.

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MYCOLOGIE MEDICALE. Communications et Rapports présentés aux Journées de Mycologie Médicale (14-15 décembre 1956) organisées par l'Institut Pasteur et la Société Française de Mycologie Médicale. 224 pp. L'Expansion Scientifique Française, Paris.

Medical mycology originated in France with the work of David Gruby more than 100 years ago. His work was brilliantly continued by Raymond Sabouraud. This book, containing the papers given at a meeting in 1956, bears witness to the fact that medical mycology is very much alive in its country of origin in the finest French tradition.

The first part deals with aspergillosis of the respiratory tract and includes interesting clinical and histopathological observations. Two cases of nasal and sinusal aspergillosis are reported. One wonders why so few cases have been reported, since the causative organisms are ubiquitous. The second chapter consists of papers on cerebral infections and their mycology. The third and largest section deals with cutaneous and systemic infections due to Candida species. The many puzzling questions in relation to these infections are discussed from almost every point of view. The chapter on dermatomycoses gives a picture of the flora of the dermatophytes not only in Paris, Lyon, Marseille and Lille but also in Africa. Other studies in Africa and Madagascar have resulted in reports on mycetoma, rhinosporidiosis, chromomycosis, and African histoplasmosis. An increasing number of cases of the latter type of histoplasmosis is being recognized, as is true of the classical form. A last paper reviews the therapy of mycotic infections.

The papers are well illustrated both in black and white and in colour and many of them include extensive bibliographies. Summaries are in English, Spanish and German.

YOUNG ENDEAVOUR. Contributions to Science by Medical Students of the Past Four Centuries. William Carleton Gibson, University of British Columbia. 292 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $7.25.

In this book the author gives short and entertaining biographical sketches of many of the past masters of research in medicine and its allied fields, with emphasis on their early scientific interests. These are arranged according to their subjects, among which it is of great interest to find a bibliography, in a chapter describing the work of John Shaw Billings (1838-1913). The work of young investigators in anæsthesia, chemistry and physics is dealt with in other chapters of the book. Throughout the book there are quotations and poems pertinent to the investigator or his work. The plates contain, as well as portraits, numerous reproductions of original sketches made by these research students to illustrate their work. There is a useful bibliography and index.

In his conclusions the author makes a plea for greater interest in and increased facilities for undergraduate medical research. His last sentence reads, "If the history summarized in these pages helps us, students and teachers alike, to be more imaginative investigators of Nature, it will have been well worth the writing."

Sir Henry Dale, O.M., has contributed a foreword to this book.

DISEASES OF CHILDREN IN THE SUBTROPICS AND TROPICS. H. C. Trowell, University College of East Africa, Kampala, Uganda, and D. B. Jelliffe, Tulane University, New Orleans, La. 919 pp. Illust. Edward Arnold Ltd., London; The Macmillan Company of Canada Limited, Toronto, 1958. $18.00.

This textbook of 900 pages is a combination of general pædiatrics and tropical diseases, with an excellent chapter on cultural backgrounds, vital statistics and standards of hygiene. The organization of the text by systems differs little from that in many texts, and what it lacks in this portion in detail is compensated for by its adaptation to requirements or conditions of the tropics.

The main body of the work is a detailed and complete résumé of tropical diseases. Over 75 authorities have contributed to the publication.

The book is an excellent up-to-date text for postgraduate students interested in tropical medicine, and for the medical missionary in the tropics. It would serve as a useful reference book for the undergraduate student or practitioner, since because of increased travel some of the so-called tropical diseases have occasionally been recognized in non-tropical countries.

DER PSYCHIATER (The Psychiatrist). Kurt Kolle, Professor of Psychiatry and Neurology, University of München. 57 pp. Georg Thieme Verlag, Stuttgart, W. Germany; Intercontinental Medical Book Corporation, New York, 1958. $1.30.

In this lecture, given at the opening of the new university psychiatric building in Kiel last year, Kolle speaks of the misunderstandings current about psychiatry, the public suspicion attached to it, and the versatility and breadth of knowledge required of the psychiatrist. He intersperses these remarks with brief surveys of landmarks in the history of neurology and psychiatry.

DEFICIENCY DISEASE. Function and Structural Changes in Mammalia which Result from Exogenous or Endogenous Lack of one or more Essential Nutrients. Richard H. Follis, Jr. 577 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $16.25.

The pathological changes, especially microscopic, produced by deficiencies of all kinds, including minerals, proteins, amino acids, vitamins (singly or in combination), lipids and carbohydrates are discussed in this book in considerable detail and in an interesting manner. Where contradictory results have been reported, the author does not hesitate to state his views. The evidence is presented fairly but not uncritically and the need for further investigation is noted frequently. There are many excellent illustrations, mostly photomicrographs, some of which would have been clearer if arrows or other distinguishing marks had been added. Quite a large number of typographical errors mar this otherwise excellent work, which includes both clinical and experimental material. The book would be useful to pathologists and investigators interested in such deficiencies. A bibliography of 1535 references is included. Ten years previously, the author published a similar book, half this size, entitled "The Pathology of Nutritional Disease".

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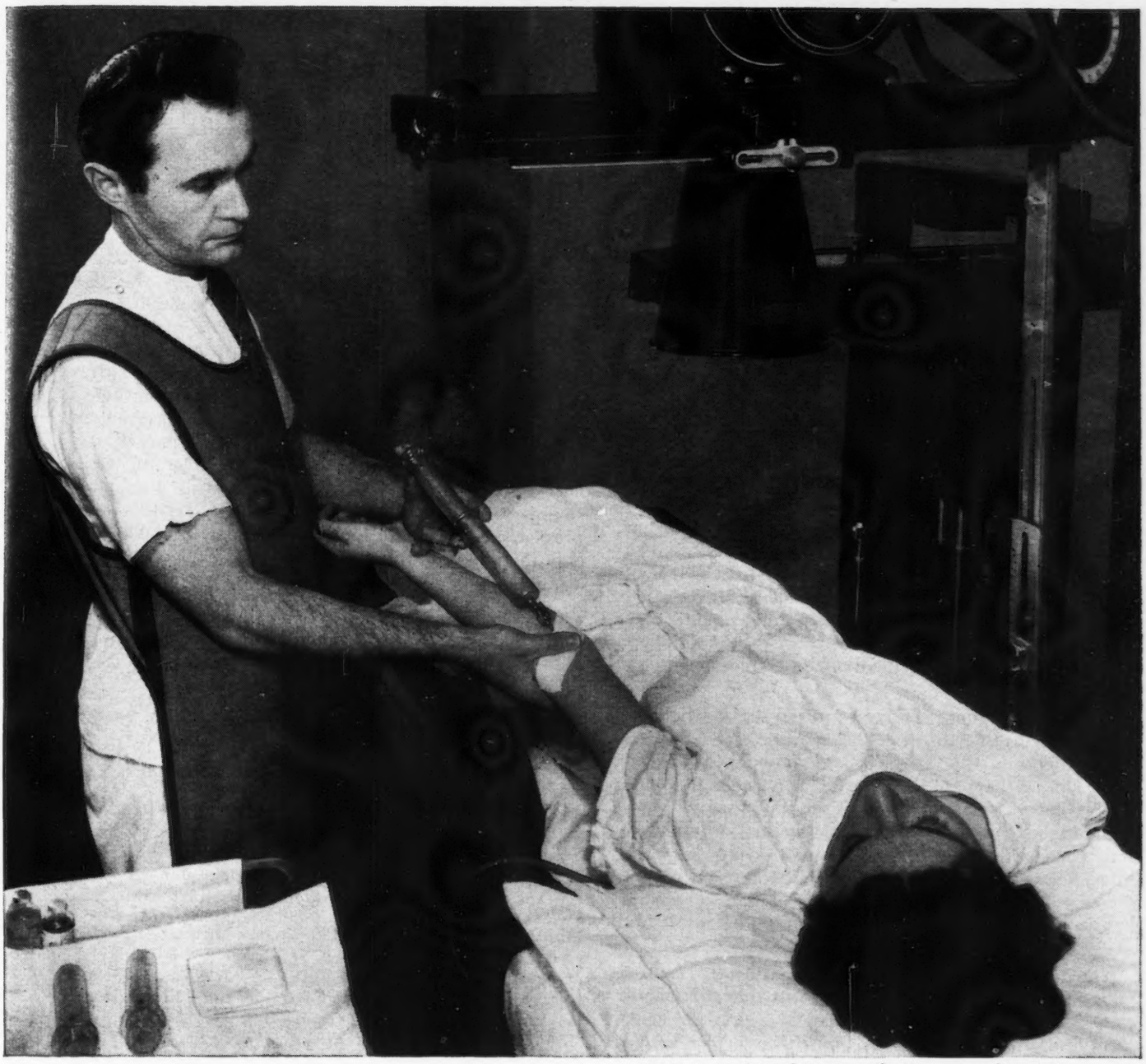

Patient receiving injection of contrast medium in preparation for nephrotomographic examination.

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BASIC CLINICAL PARASITOLOGY. David L. Belding, Boston University School of Medicine, Boston, Mass. 469 pp. Illust. Appleton-Century-Crofts, Inc., New York, 1958.

This volume is obviously an abstract of the author's larger *Textbook of Clinical Parasitology* and shows the results of abstraction by a certain unevenness in quality and value.

The first 11 pages are labelled general parasitology. They contain essentially a dictionary of technical terms woven into narrative form, with far too much unnecessary technical jargon for either the student or the practitioner. This section should have been omitted or placed at the end of the volume as a glossary of terms. The same remarks apply to much of the general introduction to each of the sections of the volume which follow.

The second section, 110 pages, discusses the protozoa. There are many errors of fact, and evidence of poor proof-reading. The illustrations are old drawings which in this day of superb photomicrography are a waste of space. There is much information which is of no use to a practitioner. The references suggest that some of the faults of this section are due to inadequate reading of literature other than American. Practitioners would do well to use any textbook of tropical medicine in lieu of this section.

The third section, 190 pages, discusses the helminthic infections of man. It is well written, accurate and informative and the diagrams and drawings are excellent. This is the best short textbook on helminthology the reviewer has ever seen. There are many tables summarizing the pathology of individual infestations and correlating the pathology with symptoms and signs. These tables are well done but the usual practitioner will have accumulated sufficient data to enable him to think in terms of symptom complexes instead of symptoms.

The fourth section, 64 pages, discusses the arthropoda, and is probably adequate for the temperate-zone student. Practitioners required to make even preliminary identification of an arthropod from this section would find it difficult. Some of the zeal displayed in classifying the protozoa and helminths should have been transferred to this section. Entomology is one part of parasitology where careful classification aids and simplifies identification.

The fifth section is a short laboratory manual, which contains useful information not found in ordinary manuals. The diagrams, photographs and charts are generally useful. The keys are too elementary for use except by junior students.

The last chapter discusses drug treatment and prevention of parasitic diseases. It is well done but is organized for ease of revision rather than ease of reading.

Only the sections of this book on helminthology and laboratory diagnoses can be recommended to the practitioner. The book seems designed for the student, and it is a pity that authors of such books insist on introducing each part with a long section of meaningless technical terms. The normal process of learning is by generalization from the particular. A student must have some facts to hang his hat on before he can begin generalizing from them. Textbooks designed for students should therefore begin each part by a clear description of a typical example. Differences from the type should follow as each parasite is described. New and necessary terms should be defined as they occur and generalizations should close the section.

THE INDIAN YEAR-BOOK OF MEDICAL SCIENCES. 483 pp. Illust. Current Technical Literature Co. Private Ltd., Bombay, 1958. sh 75.

It is a pleasure to record a major publishing activity by our colleagues in India. This book is the first annual edition of a year-book entirely compiled and edited by Indian specialists. Articles are arranged in alphabetical order, and consist of reviews of major articles in 1956 and 1957 literature, together with a list of selected references. By and large, the reviewers have done their work very well and compressed an enormous amount of information into a small space. As an example, the two reviews of amœbic and bacillary dysentery by Variava may be cited as a valuable summary of the present situation. The book is well presented and should prove extremely popular not only in India but with practitioners elsewhere wanting a quick survey of current events in medicine.

FORTHCOMING MEETINGS

CANADA

CANADIAN ANÆSTHETISTS' SOCIETY, Annual Meeting, Seigniory Club, Montebello, Que. (Dr. R. A. Gordon, Secretary-Treasurer, 178 St. George Street, Toronto 5, Ont.) May 4-7, 1959.

CANADIAN PUBLIC HEALTH ASSOCIATION, Jubilee Meeting, Sheraton Mount Royal Hotel, Montreal, Que. (Dr. G. W. O. Moss, Honorary Secretary, 150 College Street, Toronto 5, Ont.) June 1-3, 1959.

CANADIAN ASSOCIATION OF PHYSICAL MEDICINE AND REHABILITATION, Seventh Annual Meeting, Lord Nelson Hotel, Halifax, N.S. (Dr. M. Mongeau, Secretary, 6265 Hudson Road, Montreal 26, Que.) June 4-6, 1959.

CANADIAN DERMATOLOGICAL ASSOCIATION, Annual Meeting, Queen Elizabeth Hotel, Montreal, Que. (Dr. Pierre Turgeon, Regional Secretary, 837 Cherrier St., Montreal, Que.) June 4-6, 1959.

NUTRITION SOCIETY OF CANADA, Annual Meeting, School of Hygiene, University of Toronto. (Dr. G. H. Beaton, Department of Nutrition, School of Hygiene, University of Toronto, Toronto 5, Ont.) June 12, 1959.

SOCIETY OF OBSTETRICIANS AND GYNÆCOLOGISTS OF CANADA, Annual Meeting, Mont Tremblant Lodge, Mont-Tremblant, Que. (Dr. F. P. McInnis, Secretary, 280 Bloor St. West, Toronto 5, Ont.) September 10-13. 1959.

CANADIAN OTOLARYNGOLOGICAL SOCIETY (SOCIETE CANADIENNE D'OTOLARYNGOLOGIE), Annual Meeting, Sheraton-Brock Hotel, Niagara Falls, Ont. (Dr. Donald M. MacRae, Secretary, 324 Spring Garden Road, Halifax, N.S.) October 9 and 10, 1959.

OTHER COUNTRIES

INTERNATIONAL CONGRESS OF PLASTIC SURGERY, London, England. (Mr. David Matthews, Secretary General, 152 Harley Street, London W.1, England.) July 13-17, 1959.

CANADIAN MEDICAL ASSOCIATION, Ninety-Second Annual Meeting, in conjunction with the Annual Meeting of the British Medical Association, Edinburgh, Scotland. (Dr. A. D. Kelly, General Secretary, Canadian Medical Association, 150 St. George Street, Toronto 5, Ont.) July 18-24, 1959.

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MEDICAL FILMS

CONTINUING the listing of available films on medical and related subjects, we list below additional films. The films are held in the National Medical and Biological Film Library and are distributed by the Canadian Film Institute, 142 Sparks Street, Ottawa, Ontario. The evaluations have been prepared by Canadian specialists in the subjects of the films, under the Medical Committee of the Scientific Division of the Canadian Film Institute, which is headed by Dr. G. H. Ettinger.

PSYCHOLOGY AND PSYCHIATRY

Folie à Deux—1951; Sound; B & W; 15 minutes.

Produced by the National Film Board of Canada, for the Department of National Health and Welfare. Technical advisers: George E. Reed, M.D., and Heinz Lehmann, M.D., Verdun Protestant Hospital, Montreal, Que.; Charles G. Stogdill, M.D., Department of National Health and Welfare.

Mental Symptoms series, No. 9.

Description.—An instructional-record film presenting a clinical demonstration of symptoms in one of the less-common forms of mental disease, *folie à deux*, or induced insanity. The two patients are mother and daughter.

Appraisal (1952):—A good demonstration of this rare condition. The daughter's case is also a good demonstration of paranoid conditions. Should be very useful in demonstrating the condition to medical students and nurses where an actual clinical presentation is difficult or otherwise undesirable. Suitable also for general medical audiences and professional groups such as psychiatric workers (social) and psychologists. *Unsuitable for non-professional audiences.*

Availability.—National Medical and Biological Film Library ($1.50). Purchase from Distribution Branch, National Film Board of Canada, P.O. Box 6100, Montreal 3, P.Q.

Hypnotic Behavior—1949; Sound; B & W; 26 minutes.

Produced by Dr. Lester F. Beck, Department of Psychology, University of Oregon.

Description.—The film is a sync-sound cinematic record of hypnotic behaviour in two subjects, a young man and a young woman.

Appraisal (1950).—A satisfactory portrayal of hypnotic phenomena, of necessity limited to better-known manifestations. Recommended for psychiatrists and psychologists and for medical students and nurses studying in these fields. Suitable for other medical audiences, for university classes in psychology, and for interested scientific or lay groups provided a person with psychological or psychiatric training is present to lead discussion and answer questions.

Availability.—National Medical and Biological Film Library ($3.80). Purchase from Association Films Inc., 35 West 45th Street, New York 19, N.Y.

An Introduction to Clinical Neurology: Part One—1931-38; Silent; B & W; 18 minutes.

Produced by Drs. J. D. Reichard and S. Bernard Wortis, Neuro-Psychiatric Service, U.S. Public Health Service, U.S. Marine Hospital, Ellis Island, N.Y.

Description.—An instructional-record film, outlining the general neurological examination and illustrating clinical signs of disorders of the pyramidal system. (A text, prepared by Dr. Reichard, describing and interpreting the clinical material shown, accompanies this silent film.)

Appraisal (1947).—The film requires interpretation by an experienced teacher, and as a condensed summary for those who have completed their course of introductory studies it furnishes a good method of rapid review. Recommended for medical students in the clinical years and suitable for general practitioners, nurses and other medical groups. *Unsuitable for non-medical audiences.*

Availability.—National Medical and Biological Film Library ($1.50). Purchase from Psychological Cinema Register, Pennsylvania State University, State College, Pa.

An Introduction to Clinical Neurology—Part Two—1931-38; Silent; B & W; 19 minutes.

Produced by Drs. J. D. Reichard and S. Bernard Wortis, Neuro-Psychiatric Service, U.S. Public Health Service, U.S. Marine Hospital, Ellis Island, N.Y.

Description.—An instructional-record film, illustrating clinical signs of disorders of the extra-pyramidal system and of the posterior columns. A text, describing and interpreting the clinical material shown, accompanies this silent film.

Appraisal (1947).—The film requires interpretation by an experienced teacher, and is valuable as a review, particularly in centres where the considerable range of clinical material shown is not encountered. Recommended for medical students in the clinical years and suitable for general practitioners and other medical groups. *Unsuitable for non-medical audiences.*

Availability.—National Medical & Biological Film Library ($1.50). Purchase from Psychological Cinema Register, Pennsylvania State University, State College, Pa.

An Introduction to Clinical Neurology—Part Three—1931-38; Silent; B & W; 18 minutes.

Produced by Drs. J. D. Reichard and S. Bernard Wortis, Neuro-Psychiatric Service, U.S. Public Health Service, U.S. Marine Hospital, Ellis Island, N.Y.

Description.—An instructional-record film, illustrating clinical signs of disorders of the cerebellum, of the lower motor neurone, and of the convulsive state. (A text, describing and interpreting the clinical material shown, accompanies this silent film.)

Appraisal (1947).—The film requires interpretation by an experienced teacher, and the accompanying text is necessary since subtitles are not sufficiently explanatory. Valuable as a review. Recommended for medical students in the clinical years, and suitable for general practitioners and other medical groups. *Unsuitable for non-medical audiences.*

Availability.—National Medical & Biological Film Library ($1.50). Purchase from Psychological Cinema Register, Pennsylvania State University, State College, Pa.

An Introduction to Clinical Neurology—Part Four—1931-38; Silent; B & W; 18 minutes.

Produced by Drs. J. D. Reichard and S. Bernard Wortis, Neuro-Psychiatric Service, U.S. Public Health Service, U.S. Marine Hospital, Ellis Island, N.Y.

Description.—An instructional-record film, illustrating functional syndromes with pronounced physical symptoms (eleven cases), together with four miscellaneous neurological cases.

Appraisal (1947).—The film requires interpretation by an experienced teacher, and is valuable as a review, particularly in centres where the considerable range of clinical material shown is not encountered. Recommended for medical students in the clinical years and suitable for general practitioners and other medical groups. *Unsuitable for non-medical audiences.*

Availability.—National Medical & Biological Film Library ($1.50). Purchase from Psychological Cinema Register, Pennsylvania State University, State College, Pa.

Let There Be Light—1946; Sound; B & W; 58 minutes.

Produced by the Army Pictorial Services, United States War Department. Technical Adviser: Lieutenant-Colonel Michael R. Simon.

Description.—This film illustrates methods of neuropsychiatric treatment of war casualties as carried out at Mason General Hospital in the United States, at the close of World War II; it is a record film, with no staging, of actual psychiatric interviews and treatment sessions.

Appraisal (1946).—The film is up-to-date, clearly presented and recommended for doctors, medical students, nurses and social workers and health personnel actively engaged in psychiatric treatment and rehabilitation; also of interest to specialists in psychiatry. *Distribution is restricted to the above types of audiences.*

Availability.—National Medical & Biological Film Library ($3.00). For purchase apply to the Office of the Surgeon General, U.S. War Department, Washington, D.C.

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Manic State—1951; Sound; B & W; 15 minutes.

Produced by the National Film Board of Canada, for the Department of National Health and Welfare. Technical advisers: George E. Reed, M.D., and Heinz Lehmann, M.D., Verdun Protestant Hospital, Montreal, Que.; Charles G. Stogdill, M.D., Department of National Health and Welfare. *Mental Symptoms series, No. 8*

Description.—An instructional-record film, presenting a clinical demonstration of typical symptoms of the hypomanic state. A psychiatrist reviews the chief characteristics of the condition and the history of the case to be presented. The patient is then interviewed.

Appraisal (1952).—A good demonstration of the manic state. Should be very useful in demonstrating the condition to medical students and nurses where an actual clinical presentation is difficult or otherwise undesirable. Suitable also for general medical audiences and professional groups such as psychiatric social workers and psychologists. In many ways the activity around the patient during production of the film added stimuli and enabled a better demonstration of the condition than is often possible in a clinical demonstration. *Unsuitable for non-professional audiences.*

Availability.—National Medical & Biological Film Library ($1.50). Purchase from Distribution Branch, National Film Board of Canada, P.O. Box 6100, Montreal 3, P.Q.

Neurosis and Alcohol: An Experimental Study—1943; Silent; B & W; 26 minutes.

Produced by Jules H. Masserman, M.D., and K. S. Yum, M.D., University of Chicago.

Description.—A record-instructional film, presenting experiments designed to show the effects of alcohol on normal, trained cats, and on the same animals after they have been made "neurotic" by being subjected to severe motivational conflict.

Appraisal (1945).—Another film in the Masserman series on experimental neurosis. Recommended for specialists in the subject matter and for trained scientific audiences; also suitable for college and university students concerned in the subject. Previous films in the series should be seen first.

Availability.—National Medical & Biological Film Library ($3.00). Purchase from Psychological Cinema Register, Pennsylvania State University, State College, Pa.

Organic Reaction—Type—Senile—1951; Sound; B & W; 10 minutes.

Produced by the National Film Board of Canada, for the Department of National Health and Welfare. Technical advisers: George E. Reed, M.D., and Heinz Lehmann, M.D., Verdun Protestant Hospital, Montreal, Que.; Charles G. Stogdill, M.D., Department of National Health and Welfare. *Mental Symptoms series, No. 5.*

Description.—An instructional-record film, presenting a clinical demonstration of some manifestations of the organic syndrome. A psychiatrist reviews the chief manifestations of organic mental disease, noting that the organic syndrome, caused by damage of the brain tissue, is characterized chiefly by impairment of intellectual functions. Two patients are then interviewed.

Appraisal (1952).—A good demonstration of senile psychosis. Should be very useful in demonstrating the condition to medical students and nurses where an actual clinical presentation is difficult or otherwise undesirable. Suitable also for general medical audiences and professional groups, such as psychiatric social workers and psychologists. *Unsuitable for non-professional audiences.*

Availability.—National Medical & Biological Film Library ($1.00). Purchase from Distribution Branch, National Film Board of Canada, P.O. Box 6100, Montreal 3, P.Q.

Over-Dependency—1949; Sound; B & W; 32 minutes.

Produced by the National Film Board of Canada, for the Department of National Health and Welfare. Technical advisers: The Allan Memorial Institute of Psychiatry of McGill University and Royal Victoria Hospital, Montreal. *Mental Mechanisms series, No. 3.*

Description.—The purpose of this film is to illustrate the importance of fostering self-reliance in early life, and to demonstrate adult personality disabilities as a result of overprotection by parents.

Appraisal (1949).—A reasonably good film. Recommended for medical students, pre-medical students, nurses, and also for general public audiences provided a psychiatrist is in attendance for the question period. It should also be of value as a visual aid in group psychotherapy, and will have interest for such medical audiences as psychiatrists and general practitioners.

Availability.—National Medical and Biological Film Library ($3.00). Purchase from Distribution Branch, National Film Board of Canada, P.O. Box 6100, Montreal 3, P.Q.

Paranoid Conditions—1951; Sound; B & W; 13 minutes.

Produced by the National Film Board of Canada, for the Department of National Health and Welfare. Technical advisers: George E. Reed, M.D., and Heinz Lehmann, M.D., Verdun Protestant Hospital, Montreal, Que.; Charles G. Stogdill, M.D., Department of National Health and Welfare. *Mental Symptoms series, No. 4.*

Description.—An instructional-record film, presenting a clinical demonstration of some manifestations of paranoid conditions. A psychiatrist describes the chief characteristics of paranoid conditions and interviews two patients, in both of whom ideas of persecution are present.

Appraisal (1952).—A good demonstration of paranoid conditions. Should be very useful in demonstrating the condition to medical students and nurses where an actual clinical presentation is difficult or otherwise undesirable. Suitable also for general medical audiences and professional groups such as psychiatric social workers and psychologists. *Unsuitable for non-professional audiences.*

Availability.—National Medical & Biological Film Library ($1.50). Purchase from Distribution Branch, National Film Board of Canada, P.O. Box 6100, Montreal 3, P.Q.

Psychiatry in Action—1943; Sound; B & W; 68 minutes.

Produced by the Realist Film Unit, for the U.K. Ministry of Information. Technical advisers: U.K. Ministry of Health *et al.*

Description.—The film illustrates the organization and methods for the treatment and rehabilitation of patients suffering from neuroses, in one of seven U.K. hospitals established for this purpose. (*Note*: A 20-minute abridged version of this film, titled NEUROPSYCHIATRY, is available, more suitable for the general public.)

Appraisal (1946).—The long version is recommended for medical students, interns, nurses, specialists in psychiatry and psychology, and scientific audiences interested in the subject; it is unsuitable for non-scientific audiences. The short version is suitable for lay audiences.

Availability.—National Medical & Biological Film Library ($3.00). For purchase apply to the Canadian Film Institute, 142 Sparks Street, Ottawa 4, Ontario.

Psychotherapeutic Interviewing Series. Part One: Introduction—1950; Sound; B & W; 11 minutes.

Produced by Presentation Division, for the Department of Medicine and Surgery, U.S. Veterans Administration. Technical advisers: Jacob E. Finesinger, M.D., Harvard Medical School; Florence Powdermaker, M.D., U.S. Veterans Administration.

Description.—An instructional-training film, presenting an introduction to the general principles of psychotherapeutic interviewing. It is in the form of a seminar in which the instructor discusses with a group four basic principles of conducting insight therapy: (1) development and utilization of an effective doctor-patient relationship; (2) use of goal-directed planning and management; (3) focusing of material; and (4) use of minimal activity by the doctor.

Appraisal (1950).—A sound introduction to the ensuing films in this series. Recommended for medical students in the clinical years, for general practitioners and for specialists in psychiatry. Suitable for other medical audiences and allied professional groups. *Unsuitable for non-professional audiences.*

Availability.—National Medical & Biological Film Library ($1.50). Purchase from United World Films Inc., 1445 Park Avenue, New York 29, N.Y.

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CANCER SYMPOSIUM

A cancer symposium is to be held in Spokane, Washington, U.S.A., May 25-26. Participants will include some famous names in American medicine. For example, Dr. Alton Ochsner will speak on new and practical approaches to chemotherapy of cancer, while Dr. Warren Cole will speak on the future of cancer research and on perforating carcinoma of the cæcum and colon. The two-day sessions will be held at the Davenport Hotel, Spokane. Further information from Dr. John Sonneland, 104 West Fifth Avenue, Spokane 4, Washington.

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POSTGRADUATE COURSES, AMERICAN COLLEGE OF PHYSICIANS

The Committee on Postgraduate Courses of the American College of Physicians announces the following postgraduate courses:

Cardiac Arrhythmias: Philadelphia General Hospital, Philadelphia, Pa.; May 22-24.

Psychiatry for the Internist: Psychiatric Institute, University of Maryland Hospital, Baltimore, Md.; June 1-5.

Special Topics in Internal Medicine: University of Colorado Medical Center, Denver, Colo.; June 8-12.

Internal Medicine—Selected Topics: Cincinnati General Hospital, University of Cincinnati College of Medicine, Cincinnati, Ohio; June 22-26.

Further information from: The American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

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AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

Applications for certification, new and reopened, Part I, and requests for re-examination, Part II, are now being accepted. All candidates are urged to make application at the earliest possible date. Deadline date for receipt of applications is August 1, 1959. No applications can be accepted after that date.

Candidates are requested to write to the office of the Secretary for a current Bulletin if they have not done so in order that they may be well informed as to the present requirements. Application fee ($35.00), photographs, and lists of hospital admissions must accompany all applications, to Robert L. Faulkner, M.D., 2105 Adelbert Road, Cleveland 6, Ohio.

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RESIDUAL HEARING IN DEAF CHILDREN

The latest in the series of translations from foreign articles on oto-logical subjects, published by the Beltone Institute, comes from the Academy of Pedagogic Sciences, Moscow. The paper translated is entitled "Objective examination of the residual hearing of deaf children" by Sokolov and Paramonova, and in it the authors report the use of simultaneous recording of the electroencephalogram and a galvano-dermal reflex in comprehensive study of the hearing mechanism in deaf children. They found

that in the majority of deaf mutes the EEG responses were indistinct or absent; in some this was associated with absence of the galvanodermal reflex to above-threshold tones without particular significance, whereas when meaning was added to the tone stimuli the latter were heard at levels below the voluntary threshold. Comparison between the audiogram and the vibrogram showed the various possible types of correlation between auditory and vibratory sensitivity in deaf mutes. Copies of this translation may be obtained from the Editor, Translations of the Beltone Institute for Hearing Research, 2900 West 36th St., Chicago 32, Illinois.

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CATHOLIC HOSPITAL ASSOCIATION

The 44th Annual Convention of the Catholic Hospital Association of the U.S. and Canada will be held at Kiel Auditorium, St. Louis, Missouri, June 1-4. Pre-convention meetings will be held May 30-31.

The theme of this year's convention will be "Management: a sacred trust". Nationally known speakers from the health and hospital field and industry will be featured during the convention. The entire program has been designed for all hospital personnel who have supervisory responsibilities. It will develop basic general principles of management applicable to all departments in the hospital. Principles and techniques of management will be presented in terms of what they can contribute to the needs of patients and in keeping with a Christian response to these needs.

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MEDICAL SOCIETY OF THE STATE OF NEW YORK

The 1959 Annual Convention of the Medical Society of the State of New York will be held in the Hotel Statler — Hilton, Buffalo, May 9 to May 15. The general sessions, to be held on the afternoons of Monday, May 11, to Friday, May 15, will include symposia and panel discussions on surgery in cardiovascular disease, prognosis in surgically treated cancer, hypnosis in clinical practice, and the role of the general hospital in the care of special medical problems. There will be two special sessions, one on public relations on Wednesday, May 13, at 9 a.m., and one on the history of medicine, on Friday, May 15, at 9 a.m., covering the history of microscopy from its beginnings to the present. There will also be a number of section meetings. Dr. Gunnar Gundersen, President of the American Medical Association, will be the principal speaker at the annual dinner, on Monday evening, May 11. Further information from: Public and Professional Relations Bureau, Medical Society of the State of New York, 750 Third Avenue, New York 17, N.Y.

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MARKLE SCHOLARS IN MEDICAL SCIENCE

Twenty-five physicians, teachers and research workers on the faculties of medical schools in the United States and Canada have been appointed Markle Scholars in Medical Science by the John and

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Mary R. Markle Foundation, New York. Each appointment carries with it a $30,000 grant, appropriated to the medical school where the Scholar will teach and do research, to be used towards his support and to aid his research.

The two Canadian grants are to the University of Montreal Faculty of Medicine for Guy Lemieux (B.A., M.D., University of Montreal), instructor, effective July 1, 1959; currently graduate medical research fellow, National Research Council of Canada; Tufts University School of Medicine, Boston, Mass.; and to McGill University Faculty of Medicine for Huntington Sheldon (B.A., McGill University; M.D., Johns Hopkins University), assistant professor, effective July 1; currently, instructor and fellow; Johns Hopkins University School of Medicine.

In the 12 years which the fund has been making the Scholar grants, more than 250 doctors in 74 medical schools in the United States and Canada have been aided with total appropriations of $7,550,000.

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POSTGRADUATE COURSE, NEW YORK UNIVERSITY-BELLEVUE MEDICAL CENTER

The Post-Graduate Medical School of the New York University-Bellevue Medical Center offers a course in *The Physiological Basis of Clinical Electrocardiography* (an advanced course): full time, June 1 to June 5. It is designed for physicians interested in teaching electrocardiography to medical students and general practitioners.

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CHOLECYSTECTOMY FOR ACUTE CHOLECYSTITIS

The question of cholecystectomy for acute cholecystitis instead of watchful expectancy is discussed in a recent paper by Cox (*Australian & New Zealand J. Surg.*, 28: 128, 1958), who believes that cholecystotomy rather than cholecystectomy is indicated when: (1) the condition of the local tissues makes removal unsafe; (2) the physical difficulties of obesity, illumination, anæsthesia and assistance impair exposure; (3) serious local complications such as jaundice or pancreatitis call for drainage; (4) surgery must be expeditious because of age or of renal, cardiovascular, or pulmonary complications.

No conclusion is reached as to when cholecystectomy is indicated in the individual case. Operation within the first 72 hours after the onset of an attack may be technically easy but is really not necessary in most cases. The experience of the surgeon is the most important factor involved. Deterioration in the patient's condition as manifested by an increase in pain, tenderness, rigidity, pulse rate, temperature or leukocyte count should make one consider early operation, but these indications to abandon watchful expectancy are not discussed in this paper. Per-

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haps Sir Heneage Ogilvie has spoken most succinctly on this topic:

"Acute cholecystitis is seldom a surgical emergency. Operation in the acute phase is not often difficult or dangerous, but the difficulties and dangers it brings are unnecessary because such cases nearly all subside with rest and chemotherapy. While an inflamed gall-bladder can be removed easily, display of the duct junctions, identification of abnormalities, and control of the cystic artery, are less easy in œdematous tissues than in a clean field. Chest complications, sepsis, and wound rupture are more common in the immediate post-operative phase, and stricture of the duct or stones left behind, adhesions, and subdiaphragmatic infections, are seen more often than when the inflammatory reaction has been allowed to subside and the operation has been undertaken some three or four weeks later in a quiet interval."

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GASTRIC ULCER, STEROID THERAPY, AND ACHLORHYDRIA

The cause of gastric and duodenal ulcer is unknown, vascular, neurogenic and hormonal factors having been suggested in explanation. The adjective "peptic" reflects the emphasis characteristically placed on the concept that the gastric secretions produce gastric and duodenal ulcer and bring about their chronicity.

The question of the etiologic role of hydrochloric acid in the phenomenon of peptic ulcer is perennially discussed. "No acid, no ulcer" is a maxim persistently quoted, and is the justifying principle of all treatment, whether medical or surgical.

Ulcers of stomach and duodenum have developed after intracranial lesions and after burns, and ulcers during therapy with modern adrenal corticosteroids (prednisone and prednisolone) are being reported with increasing frequency. The data show that the corticosteroids increase secretion of hydrochloric acid and of pepsinogen, but even so, the question is still in doubt.

Traut (*Ann. Int. Med.*, 49: 1410, 1958) reports the case of a patient previously without ulcer, with persistent achlorhydria, who developed a gastric ulcer with the typical histopathology usually found in chronic peptic ulcer. This demonstrates that typical peptic ulcers can develop without hydrochloric acid, and that corticosteroids are capable of producing such peptic ulcers in patients with achlorhydria. According to the authors, this situation should alter our conception of the etiology of peptic ulcer.

SUBDURAL HÆMATOMA RELATED TO ANTI-COAGULATION THERAPY

Although the occurrence of bleeding into tissues or body cavities as a complication of anticoagulant therapy is well known, reports of development of subdural hæmatoma from this cause are very few. This paucity of reports may be due to the rarity of the phenomenon itself, but, because

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subdural hæmatoma is easy to detect and can frequently be treated successfully, Nathanson *et al.* (*Ann. Int. Med.*, 49: 1368, 1958) feel that presentation of an analysis of this complication is justified. They report three cases of subdural hæmatoma occurring in association with the use of dicoumarol, in two cases of myocardial infarction and one of phlebitis of the lower extremities. In one case, the patient died; probably the clinical picture was not considered to be the result of subdural hæmatoma. On the other hand, the fact that the possibility of subdural hæmatoma was thought of in the other two cases resulted in surgical confirmation of the diagnosis and subsequent cure in both patients.

The three patients developed signs and symptoms of mental and neurological disease while they were on dicoumarol therapy. In two cases there were indications of bleeding into the subarachnoid space and in the third there was xanthochromia of the spinal fluid. In the first case, the subdural hæmatoma was discovered at necropsy, and there were other hæmorrhages throughout the body. In the second case, the subdural hæmatoma was discovered ante mortem, and operation was successfully carried out. In the third case, also, the subdural hæmatoma was discovered ante mortem. The hæmatoma was evacuated but the patient died subsequently from additional intracerebral hæmorrhage. In two of the cases, it is true, the prothrombin time was markedly abnormal (56 to 71 sec.), but in the third case the value never exceeded 26 sec. compared with its control value of 12 sec.

Although no history of head trauma could be obtained, the authors could not completely exclude the possibility of minor or "trivial" head trauma as a precipitating cause of the clinical picture, hence their reluctance to classify these cases as "spontaneous" subdural hæmatoma. They feel that "minor" trauma of a type that may easily escape observation may well be capable—in patients with a tendency to bleed, especially those on anticoagulants—of initiating an exudation of blood which will then continue unchecked.

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RADIOACTIVE FAT ABSORPTION PATTERNS IN CORONARY ARTERY ATHEROSCLEROSIS

Patients with coronary atherosclerosis and hypercholesterolæmia exhibit elevated whole-blood and lipid-blood radioactivity levels that persist even 24 hours after the ingestion of an I^{131}-triolein test meal, according to Likoff *et al.* (*Circulation*, 18: 1118, 1958).

The authors consider that this radioactive fat tolerance test may become a means of detecting the presence of derangements in lipid metabolism in asymptomatic individuals, and may also be used as a guide in evaluating treatment. They feel that the reversion of an abnormal curve to normal appears to be a rational aim in any therapeutic approach to the problem of atherosclerosis.

ENZYMES AND LIVER FUNCTION

The increasing interest in and preoccupation with enzymatic activity of body tissues in general and of the liver in particular is evidenced in several reports presented at the 59th Annual Meeting of the American Gastroenterological Association in May 1958 in Washington, D.C.

Henley and his group at Ann Arbor, Mich., developed a method for obtaining morphologically intact parenchymatous cells from rat livers and assayed their content of glutamic oxalacetic transaminase (GOT) and of glutamic pyruvic transaminase (GPT). Their findings suggest that cells normally lose at least some of their enzymes by diffusion and that necrosis does not necessarily exist when serum changes are found in association with liver disease. Beta-glucuronidase activity in liver disease was studied by Pineda *et al.* in Boston, Mass., by a procedure which utilizes 6-bromo-2-naphthyl-beta-D-glucopyruronoside as a substrate. This enabled them to measure enzymatic activity in tissue homogenate, serum, and urine simultaneously with histochemical studies of enzymatic activities in tissue section. They concluded that there was significant elevation of serum beta-glucuronidase levels in patients with acute viral and drug hepatitis, and that severe liver failure may be accompanied by a precipitous fall in enzyme level. Unlike GOT, glucuronidase activity is not altered in acute myocardial infarction and this increases the value of its determination as a test of liver function.

In the discussion after presentation of the above two papers, Wroblewski (New York) emphasized that enzyme changes accompanying liver disease are not necessarily a reflection of liver function. Both he and Chalmers of Boston commented on the growing number of liver function tests, and speculated on which is the optimal clinical test available at present. Pineda replied that it is up to the clinician to decide on use of the various tests in his particular problem. He had found beta-glucuronidase determination of help in following the clinical course of hepatitis. The finding of an elevated serum glucuronidase level has enabled detection of mild or moderate cirrhosis and has confirmed hepatic dysfunction in cases in which all the other liver function tests including transaminase estimations were of little help.—*Gastroenterology*, 36: 193 and 202, 1959.

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EFFECT OF NICOTINIC ACID ON CIRCULATING LIPIDS AND CARBOHYDRATE TOLERANCE

Nicotinic acid in dosages of 3 g. daily lowered levels of serum lipid fractions in normal persons and those with elevated serum lipids according to Gurian and Adlersberg (*Am. J. M. Sc.*, 237: 12, 1959). The serum cholesterol level generally decreased more than that of the serum phospholipids. The fall in total lipids was similar to that of serum cholesterol. Individual variations were noted which could not be explained. Nicotinic acid

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consistently and significantly diminished carbohydrate tolerance in non-diabetic persons. It was then administered to patients with the adult-onset type of diabetes mellitus without significant effects on diabetic control. Further studies are necessary to evaluate the effect on patients with the juvenile type of diabetes mellitus. Serious effects were not observed.

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FIBRINOLYTIC (Plasmin) THERAPY OF EXPERIMENTAL CORONARY THROMBI

A technique was developed by Ruegsegger *et al.* (*Circulation*, 19: 7, 1959) in dogs for the production of artificial coronary thrombi, and the fate of these thrombi was followed by serial coronary arteriography. In an untreated control group of eight animals the coronary thrombus persisted in seven, while in one animal with spontaneous fibrinolytic activity the thrombus disappeared.

Significant fibrinolytic activity was then induced in eight dogs by systemic infusions of plasmin. Total lysis of the coronary thrombus was achieved in four within three to seven hours. Partial lysis (60% of more) was observed in four.

In comparison with controls of similar duration, the plasmin-treated infarcts showed less vascular congestion and œdema and decreased fibrinous epicarditis. There was also a complete absence of microthrombi, which were frequently seen only in the control hearts.

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INSULIN-TOLBUTAMIDE TREATMENT IN MATURITY-ONSET DIABETES

Combined insulin - tolbutamide treatment might benefit certain types of patients with maturity-onset diabetes of long duration, whose blood sugar was poorly controlled by insulin alone. A study of this question by Volk and Lazarus (*Am. J. M. Sc.*, 237: 1, 1959) showed that the combination allowed for a decrease in the insulin requirement, improved metabolic stability, and gave smoother control of the diabetes. This synergistic effect of insulin and tolbutamide is explained on the theory that the exogenous insulin puts the pancreas at rest while the simultaneously administered tolbutamide stimulates endogenous insulin production. Diabetic patients who respond to tolbutamide alone probably have adequate insulinogenic reserves but a defect in the normal mechanism for controlling the blood sugar by increasing insulin output.

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FOURTH INTERNATIONAL GOITRE CONFERENCE

The Fourth International Goitre Conference will be held July 5-9, 1960, in London, England, under the auspices of the London Thyroid Club and the American Goiter Association.

The American Goiter Association plans to make available to worthy candidates a limited number of

travel grants for participants in this meeting. Application blanks are available from John C. McClintock, M.D., 149½ Washington Avenue, Albany 10, New York. Applications will be received until January 1, 1960.

DETROIT DIVISIONAL MEETING, AMERICAN PSYCHIATRIC ASSOCIATION

The American Psychiatric Association has announced that a Detroit Divisional Meeting will be held in Detroit, Mich., at the Hotel Statler, October 29-31, 1959. The theme of the meeting will be "New horizons in psychiatry". Further information from: Dr. H. G. Stratton, Chairman, Publicity Committee, 14 Hanna Street East, Windsor, Ont.

MEDICAL ASSOCIATION OF SOUTH AFRICA

The 42nd Medical Congress of the Medical Association of South Africa is to be held in East London, Cape Province, South Africa, from September 28 to October 3, 1959. There will be three plenary sessions on cancer, tuberculosis and heart disease, and 17 sectional meetings. In addition, there will be the usual scientific, arts and crafts, and social meetings. Members of the Canadian Medical Association will be made welcome. Further information from Elizabeth McCabe, M.B., Organizing Secretary, Medical Congress Office, Third Floor, Ensuco House, Oxford Street, East London, Cape Province, South Africa.

POSTGRADUATE COURSES IN OTOLARYNGOLOGY

Two postgraduate courses will be offered in the fall of 1959 by the Department of Otolaryngology, University of Illinois College of Medicine:

Annual Otolaryngologic Assembly: September 18-26. A series of lectures and panel discussions. Guest lecturers will participate in a full day's program reviewing advances in and the principles of temporal bone surgery.

Course in Laryngology and Bronchœsophagology: November 9-21. Further information from the Department of Otolaryngology, 1853 West Polk Street, Chicago 12, Illinois.

THE OPEN WARD IN A PSYCHIATRIC HOSPITAL

At the beginning of 1956, an open ward policy began at the St. Lawrence State Hospital, Ogdensburg, New York. This hospital had a population at the time of about 2200 patients, many of whom had been in hospital for many years. More and more wards were opened until by the end of November 1957, 94.3% of the population at the hospital were no longer locked up by day.

In a recent paper, the Director, Dr. H. B. Snow (*Am. J. Psychiat.*, 115: 779, 1959) summarizes the very gratifying results from this policy. He points out that wards were gradually opened as and when the staff involved felt comfortable about this policy. He also notes that the development of the tranquillizing drugs was very helpful

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in the development of this program.

Where wards were opened, patients became much less obstreperous and tension diminished. The physical setup in the ward was changed; patients ceased to do damage to the furniture and fittings, and after a drop in attendance at the occupational therapy classes the attendance rose to the highest level ever. The patients paid much more attention to their appearance, and the standard of dress and toilet rose steadily. Prescribing of barbiturates or other sedatives fell enormously, since patients who were free to go out of doors slept much better. About 40% of the patients were of course on chlorpromazine or promazine. Very few patients ran away, although some confused patients were found wandering about and had to be directed back to the hospital. The family care program became greater, and the attitude of relatives changed considerably. They ceased to be suspicious of happenings behind closed doors, visited patients more readily and achieved better relationships with them. The maintenance program in the wards was easier to carry out. The community outside the hospital continued to enjoy a very good relationship with the institution. Suicides, escapes, assaults or sex problems did not present any particular difficulties. No legal complications from the new policy have accrued.

It is felt that the open ward policy relieves patients of symptoms and tensions superimposed on their original mental illness because of the locked doors, barred windows and other types of restriction.

CHRONIC BRONCHITIS IN INDUSTRY: A TRIAL OF H. INFLUENZÆ VACCINE

Because of the great frequency of chronic bronchitis in Britain as compared with other industrial European countries and with the United States, a trial was carried out by Brown and Wilson (*Brit. M. J.*, 1: 263, 1959) on volunteers to assess the value of *H. influenzæ* vaccine in reducing the incidence of relapses. Each man was studied from various standpoints to evaluate the severity of his bronchitis, and a questionnaire was completed with regard to such factors as cough, sputum, and duration of symptoms. About 79% of the volunteers had a positive skin test to the vaccine and in 24% of their sputa *H. influenzæ* was found. In all, 151 volunteers received a course of vaccine injections, and a control group was given one tablet of 3 mg. aneurine hydrochloride every morning. The course lasted from January till March 1958.

Although subjective improvement was claimed by 76.7% of the group who received injections, 73.2% of those who had received the tablets also stated that the treatment had been worth while. In both groups there were some men who claimed dramatic improvement in their ability to exert themselves. The excellent co-operation of the volunteers demonstrates the British working-man's fear of bronchitis. He is willing to do almost anything to prevent it—except give up smoking. Objectively the au-

thors were unable to demonstrate any benefit to the volunteers who received the vaccine. They suggest that in future such trials should be conducted earlier in the season and be confined to smaller groups of subjects who have been closely investigated.

ORAL METHYLTESTOSTERONE AND JAUNDICE

Foss and Simpson (*Brit. M. J.*, 1: 259, 1959) were able to collect a total of 42 cases from the literature in which jaundice was attributable to methyltestosterone administration. In one case death ensued two months after the onset of jaundice. In most cases anorexia, nausea, listlessness and lethargy with upper abdominal discomfort preceded the onset of jaundice. After withdrawal of methyltestosterone the jaundice sometimes cleared in a few days, but in other cases it lasted 1-3 months. As jaundice is a rare complication of methyltestosterone therapy and liver function recovers after withdrawal of the drug, there is no justification for withholding this form of therapy in patients requiring it for its androgenic or anabolic properties.

FRACTURE COURSE IN ONTARIO

An interesting and instructive Fracture Course will be held in Niagara Falls, Ont., on October 7, 8 and 9, 1959. This course will be provided by Sir Reginald Watson-Jones of London, England, with the assistance of Dr. Preston A. Wade of New York City.

This outstanding event will be provided by the Greater Niagara Medical Society and co-sponsored by the Surgical Section of the Ontario Medical Association.

For further particulars, see page 749 of this issue.

LONG-TERM FOLLOW-UP OF 1500 DIABETICS

Over 1500 diabetics (651 men and 896 women) under the care of the Diabetic Clinic in Tübingen, Germany, were followed up for an average of four years (1-11 years), by Buschmann, Fritze and Marsch (*German. Med. Monthly*: 4: 10, 1959). An increase in the appearance of new cases is noted after 1950 and is attributed to the change in living conditions which occurred in Germany at that time. Cases which remained latent during the war years and the post-war period of poor nutrition may have become overt cases after nutrition improved.

Of the patients, 23% gave a history of diabetes on one or both sides of their family.

Although less significant than heredity, obesity and over-eating are next in importance as precipitating factors. In 1956, of some 600 diabetics 36% were of normal weight, 53% overweight and only 11% underweight. Whilst severity of diabetes was only of slight importance in increasing the frequency of vascular complications, the duration of the disease showed a definite relationship to the incidence of complications, particularly to retinopathy. Of the total of 132

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whose diabetes was of 20 years' duration 70% had vascular disease. There was no association of complications with intake of carbohydrate, but they were twice as frequent among the overweight as among the underweight. Among those whose control of diabetes was always good, the incidence of complications was 10%, whilst those with variable or bad control had an incidence of 42-43%.

Among long-term cases 40% of the well controlled and 77% of the variably and badly controlled patients had vascular lesions. Skin disease had an incidence of 16% among men and 24% among women, whilst tuberculosis was found in 6% of men and 2% of women. Liver disease was present in 4% and 2% respectively, whilst serious dental disease occurred in less than 1% of the whole group. The death rate from tuberculosis is 2-3 times as high among diabetics as in non-diabetics, and this also points to the need for better control of diabetes.

SOCIAL PATTERNS OF ROAD ACCIDENTS TO CHILDREN

Two groups of schoolchildren and their families were compared for such personal and family characteristics as health, especially of the mother, her occupation, family size, and financial status of the family. One group was chosen from 250 children aged 5-14 who had recently been involved in non-fatal road accidents as pedestrians, and the other group was a matched control group. A social worker visited the homes of all the children, where questionnaires were completed at interview with the mother, and all the material was later coded "blind".

This study suggests that the vulnerability to accident in a child was significantly associated with one or more of the following: illness, either maternal or elsewhere in the household; maternal occupation with outside work, with other children, or with pregnancy; crowding in the household and lack of provision for protection during play. When rated according to schools, the children who had accidents were mainly found in those schools where parental standards were considered to be low.—E. M. Backett and A. M. Johnston: *Brit. M. J.*, 1: 409, 1959.

PULMONARY STENOSIS WITHOUT VENTRICULAR SEPTAL DEFECT

Contrary to earlier opinions, pulmonary stenosis without ventricular septal defect is not rare; it is estimated to occur in 10-15% of all congenital heart diseases. Grosse-Brockhoff and Loogen (*Deutsche med. Wchnschr.*, 84: 133, 1959) discuss 160 cases, which formed 10% of all the congenital lesions of the heart seen in the Düsseldorf area. The most important signs are the systolic murmur, which in cases of marked stenosis is accompanied by a thrill and prominent pulmonary conus best visualized in the right anterior oblique position on x-ray examination. Dyspnœa and tiredness on slight exertion are common in advanced cases and cyanosis in such cases has to be distinguished from the cyanosis of right-to-left shunt by determination of oxygen-saturation of arterial blood. Even though it is possible to evaluate the degree of

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stenosis present in a given case by careful clinical examination and the use of phonocardiography and the electrocardiogram (radiological examination is of less value in this respect), it is most unlikely that anybody will make a decision regarding operation without resorting to cardiac catheterization.

THE VACUUM EXTRACTOR IN OBSTETRICS

The principle of a vacuum extractor in obstetrics is already a century old. In 1905, Grauss developed forceps based on a similar idea. In 1954, in Sweden, Malmström succeeded in constructing a dependable instrument, which has been tried out in several hospitals.

The instrument consists of three different-sized suction cups to which are attached a handle, adjustable rubber tubing, and a vacuum pump.

At the Aarau Hospital in Switzerland, low forceps had not been employed except when the mother or the infant was endangered. During the last three years, in 78 such situations the vacuum extractor was employed with a fully dilated or 3-4 fingers' dilated cervix at the spine line. The conditions under which the vacuum extractor was employed included ruptured membranes and a living baby.

The use of the instrument depends on the mother's co-operation during labour, hence general anæsthesia is not applicable. If needed, oxytocic drugs such as pituitrin and pitocin are administered, and episiotomy is performed. Only if the foregoing conditions are observed can successful employment of the vacuum extractor be expected. In three cases out of 78, the use of forceps was still necessary.

The advantages of the instrument are held to be: (a) elimination of the need for extra space for the forceps; (b) avoidance of injury of the soft parts; (c) absence of brain hæmorrhage or other injury of the infant by forceps; and (d) elimination of anæsthesia.

According to experience so far, the disadvantages are: a 5% incidence of caput succedaneum, occurrence of blisters on the scalp, and a 3.8% incidence of cephalhæmatoma.

These experiments, conducted on a small scale, are not of course sufficiently convincing to permit substitution of the vacuum extractor, which has only limited application, for the satisfactory and safe low forceps technique generally in use in North America. It is hard to imagine that expectant women, pampered by the American medical technique, would give up anæsthesia for the advantages of the vacuum extractor, and that they would acquiesce readily to the high incidence of caput succedaneum and cephalhæmatoma due to the use of this instrument.

It is also unlikely that the American practitioner would return to the dangerous general employment of pituitrin and other related compounds. Further larger-scale experiments could, however, show that a more general employment of the vacuum extractor is justifiable.—H. P. Barben: *Schweiz. med. Wchnschr.*, 88: 1155, 1958.

SEQUELS OF MASSIVE HÆMORRHAGE FROM PEPTIC ULCER

Long-term studies of peptic ulcer patients who have had a severe hæmorrhage are rare. In Erlangen,

Germany, two university surgeons, Behrends and Steinhardt (*Deutsch. med. Wchnschr.*, 84: 216, 1959) have made a long-term study of 134 cases treated in 1946 to 1956. Of the 134 patients who had suffered a hæmorrhage from gastro-duodenal ulcer for the first time, 57 had a second and 15 a third hæmorrhage in the following years. One even had a fourth hæmorrhage. Of the 38 cases of acute ulcers treated conservatively, 47% had recurrent hæmorrhage. Chronic ulcers on medical treatment showed a recurrence rate of 78%, whilst all patients with acute and chronic ulcers who survived surgery (91%) remained free of recurrent hæmorrhage.

The procedure in bleeding gastro-duodenal ulcer is essentially similar to that used in perforated ulcer. In chronic ulcer, early operation is advisable if the general condition of the patient permits it. In poor-risk patients, the operation is performed after improvement has been achieved. In acute ulcer, conservative treatment has a better chance of success and gastrectomy is reserved for cases where medical treatment has failed or where hæmorrhage recurs.

THIORIDAZINE (MELLERIL): ITS PHARMACOLOGY AND CLINICAL USE IN PSYCHIATRY

Thioridazine (Melleril-Sandoz) is a new derivative of phenothiazine and has the following formula: 3 - methyl - mercapto - 10 - [2′ - (N - methyl - piperidyl - (2″)) - ethyl - (1′)] - phenothiazine.

Taeschler and Cerletti describe its pharmacology (*Schweiz. med. Wchnschr.*, 88: 1216, 1956) and in the same issue there is a paper by Remy on the effects of this drug in clinical psychiatry.

In experiments with white mice, whose activity was measured by having them interrupt a beam of a photoelectric cell in walking about the cage and counting the number of these interruptions per unit of time, it was found that thioridazine decreased their activity only slightly. If however the mice were previously made overactive by administration of amphetamine, thioridazine had a marked inhibitory effect on this overactivity. Hungry mice which had to cover nine metres in order to reach their food were found to cover the distance in almost the same time with or without thioridazine when fed at the regular time. When, however, they were offered the food at a time different from their usual feeding time, thioridazine had a very marked slowing effect on the time they required to reach the food. When mice were exposed to a secondary stimulus producing a conditioned reflex without the original reinforcing stimulus (electric shock), thioridazine was able to inhibit the reaction considerably, but it had little or no effect if the mouse was subjected to both stimuli. All these experiments indicate to the authors that thioridazine inhibits mainly the useless and unphysiological motor activities and that its effect on useful and protective activities is much less pronounced.

In vitro experiments show that the adrenolytic action of the drug is 1.8 times greater than that of dihydro-ergotamine. It reduces the mydriatic effect of morphine by some 50% but does not influence pupils dilated by anticholinergics. On the other hand, it potentiates the analgesic effect of morphine. The inhibiting effects on the neurovegetative system indicate a cen-

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tral rather than a peripheral effect. When compared with chlorpromazine, it requires ten times larger doses than the former to produce catalepsy, and hypothermia is much less depressing on the motor activity of normal mice and rats and has only a slightly weaker effect than chlorpromazine on the neurovegetative system.

Remy has used thioridazine since November 1956, and reports his experience with this drug in the treatment of 152 patients. The majority were chronic patients and all were resistant to insulin and electroshock therapy; 94 schizophrenics, five manic-depressives, 17 psychopaths with behaviour disorders, 29 agitated oligophrenics, one paranoid and one organic psychotic made up the treated group. Of this total, 78% were improved, a percentage similar to the one achieved with chlorpromazine. The superiority of thioridazine to chlorpromazine becomes evident when one compares their effects on agitated states with delirium and particularly on depression with negativism. Of those who failed to improve on chlorpromazine, some 75% obtained improvement on the new drug. Remy presents five case histories demonstrating typical effects of this drug. Of the whole group, 25 patients who had hitherto been considered hopeless were discharged on this drug and so far none of them has relapsed. The unpleasant side effects which are not infrequent with the other phenothiazine derivatives, notably somnolence, icterus, allergic reactions and extrapyramidal disorders, were not observed in any of the cases treated.

POSTGRADUATE SURGICAL TOUR OF EUROPE

The International College of Surgeons will conduct a midsummer postgraduate tour. Dr. Ross T. McIntire, executive director, will be the co-ordinator. Countries to be visited are The Netherlands, Denmark, Norway, Sweden, Finland, Russia, Austria, Germany, and France. Departures will be from New York July 17 on the S.S. *Nieuw Amsterdam* or by plane July 24. Tour participants will take in the Amsterdam meeting of the I.C.S., July 25-26, and the Helsinki meeting, August 8-9; spend three days in Leningrad, August 11-13, and three days in Moscow, August 15-17; and meet with the fellows of the I.C.S. in Vienna, August 19-20.

Plane passengers will return to New York on August 27 and boat passengers will arrive September 2.

For further information, write to Dr. Ross T. McIntire, executive director, International College of Surgeons, 1516 Lake Shore Drive, Chicago 10, or the International Travel Service, Inc., 119 South State Street, Chicago 3.

ANNUAL MEETING OF THE NATIONAL TUBERCULOSIS ASSOCIATION

The 55th Annual Meeting of the National Tuberculosis Association will be held May 25-28 at the Palmer House, Chicago, in conjunction with the 54th Annual Meeting of its medical section, the American Trudeau Society, and the 47th Annual Meeting of the National Conference of Tuberculosis Workers. At the opening medical session on Monday morning, May 25, papers will be presented in the fields of clinical tuberculosis and

pulmonary physiology (the latter under the chairmanship of Dr. David Bates, Montreal). The program for the afternoon session will include a symposium on pulmonary emphysema and papers on differentiation of mycobacteria. On Tuesday morning there will be a series of contributions on nontuberculous pulmonary disease and on tuberculosis research. The Amberson Lecture will be given by Dr. Frank L. Horsfall, Jr., of New York, who will speak on problems and progress in viral infections in man. The afternoon session will have papers on respiratory disease research, experimental methods, and tuberculin testing. At the medical section meeting on Wednesday morning, May 27, a presentation of long-term studies in BCG vaccination in Chicago will be followed by a discussion of current concepts in the surgical treatment of cardiac lesions, and the Robert Keeton Memorial Lecture will be given by Dr. Charles M. Fletcher of London, England, whose subject will be chronic bronchitis. From 2 to 4 p.m. on Wednesday there will be a symposium on smoke, smoking, and chest diseases.

In addition to the medical section meetings, there will be public health sessions and nursing sessions on Monday, Tuesday and Wednesday, May 25-27.

Further information from: National Tuberculosis Association, 1790 Broadway, New York 19, N.Y.

THE LEGAL ENVIRONMENT OF MEDICAL SCIENCE

The hodge-podge of laws and regulations now governing medical research obstructs and imperils progress in the life sciences, according to Dr. Lester R. Dragstedt, President of the National Society for Medical Research and Professor of Surgery at the University of Chicago School of Medicine. To bring order into this chaotic situation, the Society, in conjunction with the University of Chicago, has called the first National Conference on the Legal Environment of Medical Science. The meeting will be held May 27 and 28 on the University of Chicago campus.

Physicians, scientists, and lawyers are confused over legal rights and responsibilities towards human beings serving in trials of new medical treatments. Practical problems such as access to cadavers and obtaining animals for humane use in laboratories, according to Dr. Dragstedt, have stimulated the Society, whose membership includes all the accredited medical schools and most medical research associations, to issue a call for clarification of standards.

The conference will focus on three major fields: medical experiments on human subjects, medical studies involving the use of dead human bodies, and medical experiments on animal subjects. The conference will attempt to reach agreements on ethical standards for the experimental use of human volunteers, cadavers, and laboratory animals, and will also seek to develop principles for a model legal code to govern research in medicine. Participants will include scientists, legal scholars, religious leaders, and representatives of various groups affected by differing practice, decisions and laws, which have grown up over the years.

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The conference is an outgrowth of an N.S.M.R. standing committee under Dr. Oliver P. Jones, head of the anatomy department of the University of Buffalo Medical School. The committee was established originally to investigate shortages of cadavers for anatomical studies.

Inquiries relating to the conference should be addressed to the National Society for Medical Research, 920 South Michigan Avenue, Chicago 5, Illinois.

CLINICAL DEATH

Progress in resuscitation techniques has given rise to situations unheard of in the past, some of which entail delicate problems of ethical and medico-legal responsibility. A point raised by Wertheimer, Jouvet and Descotes of Lyon (*Presse méd.*, 67: 87, 1959) has to do with the question of when artificial respiration can be stopped. Some comatose patients linked to a respirator are illustrations of that well-known saw of being "biochemically well but clinically dead". In these cases it could be more appropriate to talk about being "cardiologically alive" since such a patient is motionless, has no more deep or superficial reflexes, offers no response to painful stimuli, and has dilated atonic pupils and regular pulse, usually at about 100 per minute. The body temperature is usually below normal, and the renal function persists provided intravenous infusions are running. Except for the pulse the only sign of life is the heaving of the chest in accordance with the activity of the respirator.

Presented with a number of these cases, the authors have looked for a criterion determining the point at which attempts at resuscitation become futile. They finally settled on signs of electrical activity in the central nervous system, on the basis that there was no point in carrying out resuscitation techniques if the brain was irreversibly out of commission. As scalp electrodes pick up only variations of potential of a certain intensity, it was decided to investigate the deeper structures of the brain by means of fine sterile bipolar electrodes introduced through trephine holes towards the thalamus. In one of the cases where the procedure was carried out, encephalomalacia was noted when the brain substance began oozing from the holes. The routine which the authors have now adopted consists in providing electrical stimulation to the large nerve trunks, the thalamus and the cortex, and declaring the patient dead in spite of heart action if no response obtains. It has been noticed that bulbar stimulation through compression of the carotid arteries or the eyeballs fails to alter the cardiac rhythm in a number of patients who for all practical purposes have become heart-lung preparations. On occasion, an acceleration of the pulse was obtained by the intravenous injection of dextro-amphetamine in large doses.

INTERNATIONAL CONGRESS ON PHLEBOLOGY

An International Congress on Phlebology will be held in France in the town of Chambéry, Savoie, on May 6, 7 and 8, 1960. The main subjects to be discussed at this Congress will be venous stasis, pain in venous affections of the lower limbs, and extravascular applications of sclerosing techniques. The

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official languages of the Congress will be English, French, German, Italian and Spanish, with simultaneous translation. Further information from the French Society of Phlebology, 63 Boulevard des Invalides, Paris 7, France.

ASPIRATION PNEUMONIA

Aspiration pneumonia is a pulmonary problem presenting a great deal of diagnostic difficulty and frequently neglected in the differential diagnosis of pulmonary lesions. It may result from aspiration of oils, food and gastric secretions, foreign bodies, and infected materials. It has a tendency to localize in the most dependent portions of the lungs at the time of aspiration.

Lipoid pneumonia should be considered in all basal pneumonic processes of undetermined etiology. The major difficulty, according to Besman and Lyons (*Dis. Chest,* 35: 6, 1959), is when the lesion (paraffinoma) resembles neoplasm. Clinical, radiological, and cytological approaches are necessary for establishing a diagnosis. Aspiration of gastric contents results in pulmonary œdema early and may cause acute bronchial obstruction. Later, foreign body reaction occurs and leads to chronic bronchial obstruction and pulmonary fibrosis. Pathological changes in the lung after aspiration of a foreign body depend on the site of lodgement, chemical and physical characteristics of the foreign body, and length of time elapsing before its removal. There is a whole range of aspiration pneumonias due to inhalation of infected material from the mouth and throat, varying in severity from solitary lung abscess and a predominant pneumonic process to less severe forms of respiratory tract infections. Aspiration of infected material from the mouth and throat occurs in patients with poor dental hygiene and with poor or absent gag reflexes due to states of unconsciousness. This is most commonly seen in alcoholics.

DIAGNOSIS OF GASTRIC LESIONS

A study of 1250 gastric lesions treated at the Presbyterian Hospital in New York was undertaken by Hennig and Harvey (*Ann. Int. Med.,* 50: 43, 1959) to determine the frequency with which the clinician finds himself confronted with the problem of a gastric lesion of questionable nature. The series included 650 carcinomas, of which 299 were resectable. Among these 299, a total of 150 represented the categories "fungating" or "mixed". These 150 included 19 not diagnosed as carcinomas preoperatively. Among the 351 nonresectable carcinomas, 45 were not diagnosed before operation.

The problem of ulcerative lesions proved more difficult. The 600 ulcers ultimately recognized as benign were included in the category of questionable malignancy at the time of first examination. Furthermore, these total series included 105 resectable malignancies of the classes designated as "penetrating" or "superficial diffuse", and as "linitis plastica", in which ulceration was a prominent feature. Of these, 44 were not diagnosed preoperatively. The diagnosis was considered as question-

able in a total of 708, that is, in 57% of the complete series of 1250 gastric lesions.

Individual case reports are presented to illustrate the difficulty of diagnosis of gastric lesions preoperatively, as well as at operation when the lesion is directly exposed to the surgeon's view. The cases of resectable carcinoma which originally appeared to be benign had a more favourable prognosis than the total group of resectable carcinomas.

The authors consider that conservative treatment can be used in selected patients with a minimal margin of error, provided that all the known methods of diagnosis are utilized. The risk inherent in this policy is no greater than the risk taken in the resection of all gastric ulcerations. If any of the diagnostic studies — roentgenography, gastroscopy, cytology, etc. — support the suspicion of malignancy, and especially if healing of a gastric ulceration is not prompt, complete and permanent, surgical intervention is usually indicated. The importance of frozen sections at the time of operation is evaluated.

CHANGE IN CLINICAL PATTERN OF ACUTE LEUKÆMIAS

True spontaneous change in the clinical pattern of any disease (pathomorphosis) is rare. The usual reasons for the apparent change in the course of a given disease are the increase in frequency of variants, and the effects or side effects of treatment by drugs. Many such apparent changes have occurred in acute leukæmia, as is shown by Bock (*Deutsche med. Wchnschr.*, 84: 293, 1959), who compared the age distribution, survival time and clinical features of the disease in the Marburg (West Germany) area in 1920-1955 (185 cases) with his own 90 cases observed during 1945-1948. The incidence of acute leukæmia was one-fifth that of chronic forms, but has now become equal to the latter; it is now far more common among adults than before. Survival time has doubled, and many unusual symptoms and signs have appeared.

The variety of complications that can nowadays occur in a single case of acute leukæmia is illustrated by the case of a 46-year-old woman who survived for two years during which she had three remissions, suffered from various hæmorrhages, vulvitis, phlebitis, tonsillitis, pyoderma, pleurisy, mycotic infection, Cushing's syndrome, perforation of the small bowel and miliary spread of the disease through the lungs.

However, all these changes can be explained by earlier diagnosis, antibiotic and steroid therapy and their side effects, longer survival, and longer periods of observation. There is no good evidence that true spontaneous change in the pattern of acute leukæmia has taken place.

BOOSTER DOSES OF POLIO VACCINE

It has already been reported by the British Medical Research Council that the response of children under 10 years of age to a third or booster dose of British polio vaccine is mainly satisfactory, with large rises in antibody titres to all 3 virus types, although a few failed to produce high levels of type 1.

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A recent paper in the *British Medical Journal* (1: 609, 1959) reports studies of booster doses in adolescents and adults. The booster dose was given to 111 adolescents and adults 6 to 12 months after primary immunization, and produced a good response to types 2 and 3. At the time of the booster dose, all but four subjects still had detectable antibody induced by their initial immunization, although with type 1 one-third had lost their antibody and gave a comparatively poor response to the booster dose. In these persons with a poor response, however, a fourth dose appeared to produce a booster response to this type. It is suggested that, in the age groups studied, at least a three-fold increase in the amount of type 1 antigen in the polio vaccine will be necessary to give satisfactory antibody responses after three doses in all subjects.

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ACUTE APPENDICITIS WITHOUT OPERATION

In a busy Russian hospital, no fewer than 13,029 patients were admitted to hospital between 1952 and 1956 for acute appendicitis. Of this number, 6.35% (828 patients) were not operated upon, and of these 236 were not operated on because there was already an infiltrate present.

Murlaga (*Klinicheskaya Meditsina*, 2: 76, 1959) reports on a follow-up of 226 patients who were not operated upon and who were contacted between six months and six years after the event. Only 40 persons out of this number had remained well and free from pain; 123 patients had subsequently been operated upon, usually for another acute attack, while 63 patients still complained of abdominal pain.

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A UNION OF LIBERAL PROFESSIONS

The organ of the Swiss Medical Association (*Schweiz. Arztezeit.*, 40: 155, 1959) reports an interesting development in Switzerland, where a confraternity of the liberal professions has been formed, with the General Secretariat of the Swiss Medical Association as the co-ordinator. The confraternity includes the following professional associations: lawyers, pharmacists, engineers and architects, veterinarians, dentists and physicians. Representatives of the various organizations of the liberal professions met about a year ago to discuss closer co-operation among the various professions. The question of formation of an inter-professional organization with a secretariat was discussed and rejected. It was felt that more good could be obtained through meetings of representatives of the various associations from time to time, in order that the various professions should get to know each other better. When problems of common interest arose, the various organizations would be better able to co-operate with each other in solving them. The appropriate government departments have been informed of the existence of this confraternity. As a step to informing the medical profession of the problems existing in other liberal professions, the journal prints a short account of the present position of each of these professions in Switzerland. This is an example which might well be copied in other countries.

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A GREAT CANADIAN SURGEON

The early surgeons of Canada, from the pioneers of the east and west to the founders of the schools and hospitals, are the subject of a series of articles in the historical section of the *Canadian Journal of Surgery*. The seventh article in this series which appears in the April issue of the Journal is written by Dr. Edouard Desjardins of Montreal, who describes the life and work of Sir William Hales Hingston (1829-1907)

William Hingston won respect not only as a surgeon and teacher, but as a leading citizen of Montreal. As a surgeon, he was one of the first Canadians whose fame spread beyond Canada to Europe and the United States. As a citizen of Montreal he was for three years the vigorous Mayor of the city, particularly concerned to raise the standards of hygiene of the time.

He was the son of an Irish-born lieutenant in the British Army who settled down to the life of gentleman farmer on a piece of land on the banks of the Chateaugay river. Straitened family circumstances led to an interruption of William's education at the Collège de Montréal and he became for a time an apprentice pharmacist. Characteristically, he worked in the pharmacy by day and studied at night until he had prepared himself to enter the University of Montreal. He graduated as a doctor of medicine in 1851 and continued his studies in Europe and Britain during the next two years.

His reputation was already established when he returned to Canada, and he very soon was attached to the Hôtel-Dieu Hospital in Montreal which he continued to serve as surgeon, and for forty years as surgeon-in-chief.

One of the many interesting developments in which Sir William played a leading part was the progress of medical education in Montreal, and Dr. Desjardins describes the unusual and unsatisfactory situation which existed when the city had no less than three medical schools. The union of Victoria College and Laval University was the diplomatic solution to the problem which Sir William helped to bring about.

The many other activities of this outstanding man are described by Dr. Desjardins, and the reader is left with a picture not only of the man but of his times. The illustrations taken from the collection of the Hôtel-Dieu Hospital add interest to the account.

Previous articles in the History of Canadian Surgery series have dealt with Francis Shepherd, Edward Archibald, Alexander Primrose, George Alexander Kennedy, Frank Hamilton Mewburn and George Armstrong Peters.

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INDUCTION OF SARCOMA IN RATS BY IRON

Iron has not been considered carcinogenic in the past, but Richmond (*Brit. M. J.*, 1: 947, 1959) describes experiments in rats which suggest that iron-dextran complex injected weekly or twice a week will cause sarcoma to develop at the site of intramuscular injection. In one experiment, 16 out of 23 rats developed such a tumour at the site of injection between the 11th and 16th months of the experiment, while in another in which rats were given injections twice a week for 12 weeks, a sarcoma subsequently developed. There was no result after injection of dextran-saline, or after giving saccharated oxide of iron. The change at the site of injection in the early stages was a progressive accumulation of histiocytes laden with iron pigment. Metastases were not observed.

The clinical significance of these observations is not immediately obvious, since the dosage used in the experiments was massive (200- to 300-fold the therapeutic dose). These findings might be related to the fact that there is a special tendency for the cirrhosis of hæmochromatosis to undergo malignant change, and to the development of lung cancer in hæmatite miners.

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PANIC AND PHOBIA

A possible method of treating states of panic and phobia is outlined by Malleson (*Lancet*, 1: 225, 1959). He suggests that instead of trying to avoid the object of his phobia, the patient should face up to it and try to experience the maximum amount of fear and the concomitant sensations, as a regular thing. Thus a patient with agarophobia is told to go outside his front door, experience all the fear possible there, and then advance 25 yards or so down the pavement or until the fear arises again. He is then to stand still and experience his emotions once more, and so on. Malleson states tht among his patients, a small amount of assiduous practice has reduced such phobias to manageable proportions and has sometimes freed ordinary life from much restriction.